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VOLUME 45 NUMBER 5

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PROTHROMBIN AND HEPATIC FUNCTION

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AND

ORMAND C. JULIAN, M.D.

CHICAGO

It is now well established that prothrombin is continuously formed in the normal liver in the presence of adequate vitamin K. In 1938 Warner [1] observed that partial hepatectomy in the rat resulted in a decrease in the prothrombin content of the blood. Warren and Rhoads [2] reported in 1939 that after hepatectomy in dogs the plasma prothrombin fell to less than 20 per cent of normal within twelve to eighteen hours. Other evidence implicating the liver as a site of prothrombin production has been presented by many workers.[3] These investigators produced damage to the liver by giving animals various hepatoxins and observed a fall in plasma prothrombin.

There is also ample evidence at hand which points to the liver as the source of prothrombin in man. In patients with hepatic disease the prothrombin level is frequently down, and the giving of vitamin K to these patients either does not alter the prothrombin or does so slowly.[4] This

From the Department of Surgery, the University of Chicago.

This work was aided by grants from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, J. Exper. Med. **68**:831-835 (Dec.) 1938.

2. Warren, R., and Rhoads, J. E.: The Hepatic Origin of Plasma Prothrombin, Am. J. M. Sc. **198**:193-197 (Aug.) 1939.

3. Cullen, S. C.; Ziffren, E. S.; Gibson, R. B., and Smith, H. P.: Anesthesia and Liver Injury, J. A. M. A. **115**:991-993 (Sept. 21) 1940. Lord, J. W., Jr.: Effect of Trauma in the Liver on Plasma Prothrombin, Surgery **6**:896-898 (Dec.) 1939. Allen, J. G.; Kable, V., and Livingstone, H.: Effects of Anesthetic Agents on Prothrombin Concentrations in Experimental Animals, Anesth. & Analg. **20**: 156-159 (May-June) 1941.

4. (*a*) Pohle, F. J., and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, J. Clin. Investigation **19**:365-372 (March) 1940. (*b*) Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, Proc. Soc. Exper. Biol. & Med. **41**:559-561 (June)

(Footnote continued on next page)

response is in sharp contrast to the rapid return of prothrombin to normal in patients with obstructive jaundice or biliary fistula. In the group with primary liver damage the reduced prothrombin is not due to inadequate vitamin K but to the inability of the liver to utilize the vitamin and form prothrombin.

Attention has recently been focused on hepatic function and prothrombin deficiency in an attempt to correlate liver disease with the prothrombin content of the blood. Wilson [4b] concluded that the prothrombin time was closely correlated with the excretion of hippuric acid of patients with liver disease. These results have not been generally confirmed.[5] Most workers are agreed that a crude relation may exist between hippuric acid excretion and blood prothrombin but that the extent of hepatic impairment as reflected by these two values is seldom in close agreement. Moreover, prothrombin production is but one of many functions of the liver, and experience has shown that these various functions are seldom, if ever, equally affected by hepatic injury. This fact serves to limit prothrombin deficiency as a measure of quantitative liver damage.

In 1940 we called attention to the fact that prothrombin deficiency resulting from the faulty absorption of vitamin K, as in cases of biliary fistula or obstructive jaundice, responded rapidly to vitamin K therapy, while prothrombin deficiency from primary liver damage either failed to respond to the vitamin or did so at a slow rate.[6] These observations formed the basis for a subsequent report that same year, in which we suggested that one could differentiate between intrahepatic and obstructive jaundice by the prothrombin response obtained when vitamin K and bile salts were administered.[4d]

In cases of extrahepatic obstructive jaundice the decreased prothrombin in the blood returns to the normal level in twenty-four to thirty-six hours after the oral administration of vitamin K and bile salts. A more prompt response may be obtained by the parenteral administration of suitable preparations. On the other hand, when reduction of

1939. (*c*) Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: Use of Serial Dilutions in Determination of Prothrombin by the One-Stage Technic, Arch. Surg. **41**:873-878 (Oct.) 1940. (*d*) Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, ibid. **41**:1363-1365 (Dec.) 1940.

5. Kark, R.; White, F. W.; Souter, A. W., and Deutsch, E.: Blood Prothrombin Levels and Hippuric Acid Excretion Liver Function Test in Liver Disease, Proc. Soc. Exper. Biol. & Med. **46**:424-426 (March) 1941. Lucia, S. P., and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, Am. J. M. Sc. **201**:326-340 (March) 1941. Allen, J. G.: Unpublished data.

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prothrombin is due to impairment of function and organic liver damage, either no response is secured by vitamin K therapy or the recovery is markedly delayed and incomplete.

Since our original report on this phase of the problem, reports by Andrus and Lord,[7] Olwin [8] and Kark and Souter [9] have confirmed our

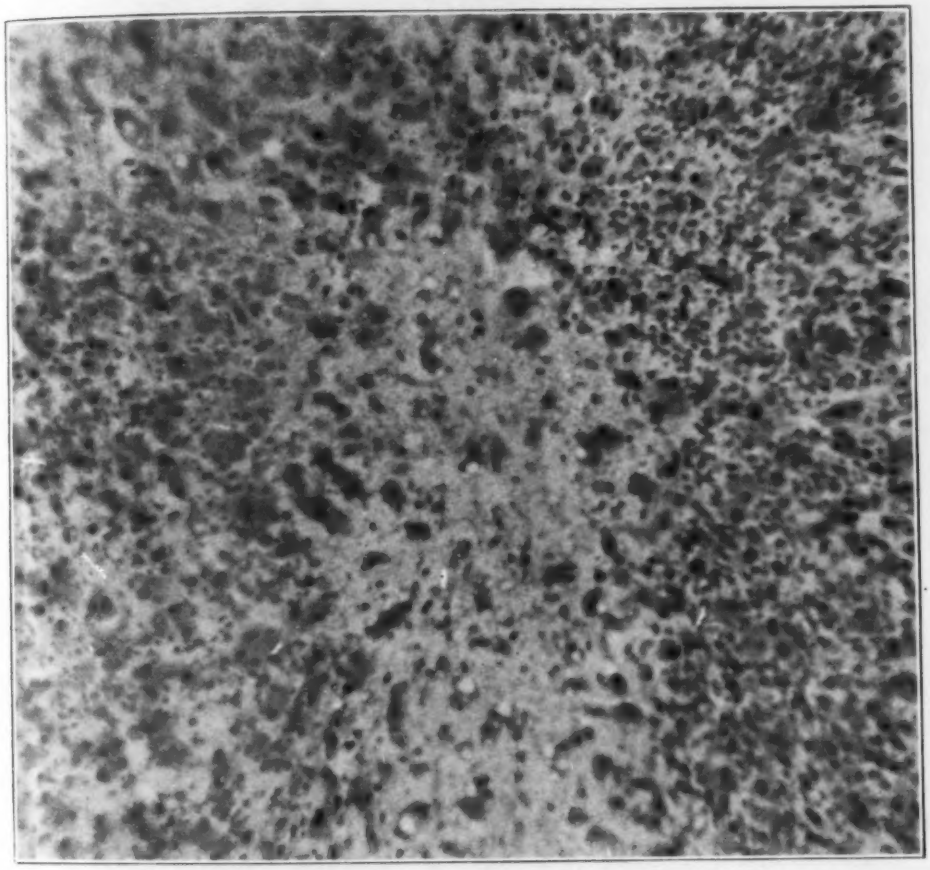

Fig. 1 (case 2, table 1).—Photomicrograph of the liver of a patient with obstructive jaundice and extensive secondary liver damage whose prothrombin deficiency was readily corrected with vitamin K.

7. Lord, J. W., and Andrus, W. W.: Differentiation of Intrahepatic and Extrahepatic Jaundice, Arch. Int. Med. **68**:199-210 (Aug.) 1941.

8. Olwin, J. H.: Differentiation of Surgical Jaundice from Severe Damage of the Liver (Subacute Yellow Atrophy) Clinically Simulating It, Arch. Surg. **43**: 633-644 (Oct.) 1941.

9. Kark, R., and Souter, A. W.: Response to Vitamin K: Liver Function Test, Lancet **2**:693-696 (Dec. 6) 1941.

observations and have indicated also the significance of the prothrombin responses to vitamin K in the jaundiced patient. This prothrombin response to vitamin K has now been used in this clinic for two years as a diagnostic procedure. Other cases to be presented here have now been studied; the results obtained in these extend and confirm our previous report.

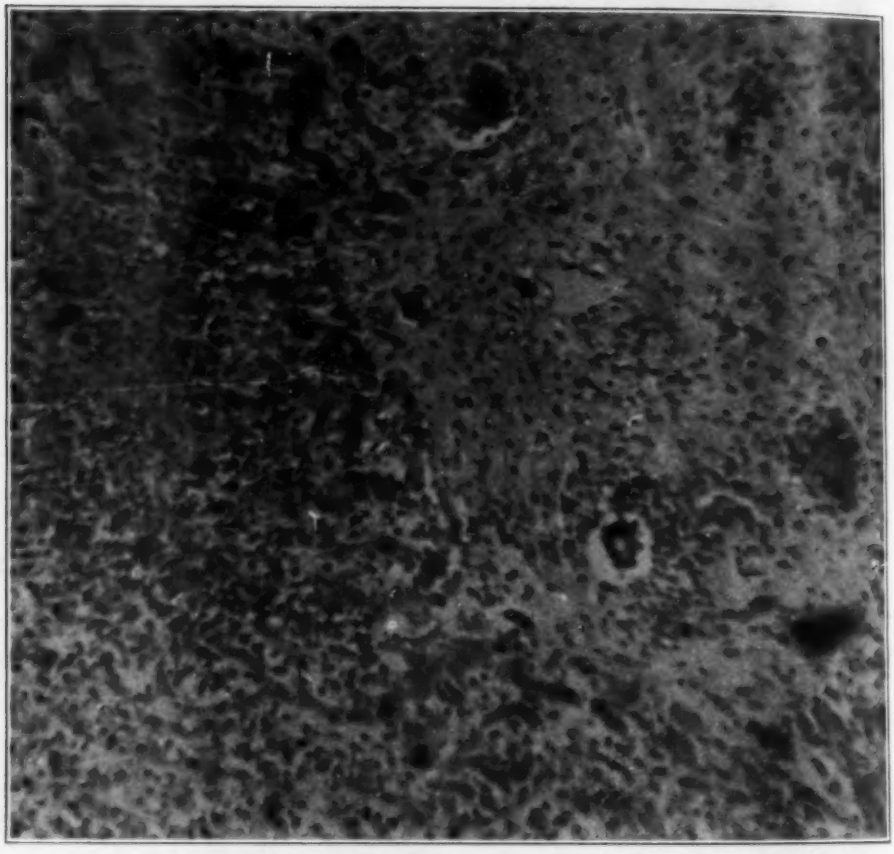

Fig. 2 (case 6, table 1).—Photomicrograph of the liver of a patient with obstructive jaundice and extensive secondary liver damage whose prothrombin deficiency was readily corrected with vitamin K.

REPORT OF CASES

Seven Patients with Obstructive Jaundice; Sections of the Liver Were Made Either at Operation or at Autopsy (table 1).

Case 2.—The patient had stricture of the common duct for four months. At autopsy a moderate degree of periportal fibrosis was present. This patient responded readily to vitamin K, indicating that the liver damage secondary to

obstruction of the common duct was not sufficient to impair the production of prothrombin.

Case 4.—The patient died after drainage of the common duct for choledocholithiasis and stricture. The liver weighed 1,950 Gm. and was light yellow-gray. The cut surface showed enlarged lobules. Section displayed chronic pericholangites with definite biliary cirrhosis. Parenchymal cells were flattened, and atrophic canaliculi were often plugged by inspissated bile.

Table 1.—*Rapid Prothrombin Response of Patients with Obstructive Jaundice to the Administration of Vitamin K*

Case	Diagnosis	Prothrombin (Per Cent) Initial	Prothrombin (Per Cent) 24 Hr. After Therapy	Daily Dose of Vitamin K (Mg.)	Comments
1	Stone in the common duct	45	100	8*	Icterus
2	Stricture of the common duct	15	100	8*	Icterus
3	Fistula of the common duct	55	100	8*	.....
4	Stone in the common duct	43	100	8*	Icterus
5	Stone in the common duct	63	100	8*	Icterus
6	Carcinoma of the pancreas with obstruction of the common duct	33	100	8*	Icterus
7	Stone of the common duct	28	100	8*	Icterus
8	Fistula of the common duct	35	100	8*	.....
9	Carcinoma of the head of the pancreas	66	100	8*	Icterus
10	Carcinoma of the head of the pancreas	28	100	8*	Icterus
11	Carcinoma of the head of the pancreas	56	100	8*	Icterus
12	Stricture of the common duct	61	100	8*	Icterus
13	Stone in the common duct	82	100	8*	Icterus
14	Carcinoma of the common bile duct	43	100	8*	Icterus
15	Carcinoma of the ampulla of Vater	58	100	8*	Icterus
16	Duodenal ulcer	70	100	10†	Liver normal at operation; no icterus
17	Fistula of the common duct	55	100	10†	.....
18	Carcinoma of the head of the pancreas	86	100	10†	Icterus
19	Carcinoma of the head of the pancreas	74	100	10†	Icterus
20	Fistula of the common duct	56	100	100	.....
21	Carcinoma of the ampulla of Vater	54	100	10†	Liver 8 cm. below the costal margin; icterus
22	Stone in the common duct	45	100	10†	Liver palpable at the costal margin; icterus
23	Stone in the common duct	85	100	10†	Liver 5 cm. below the costal margin; icterus
24	Stone in the common duct	65	100	10†	Icterus
25	Carcinoma of the common duct	58	100	10†	Liver 6 cm. below the costal margin; icterus
26	Carcinoma of the common duct	65	100	10†	Icterus

* Patient was given 2-methyl-1, 4-naphthoquinone.

† Patient was given tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester.

Case 6.—The patient had carcinoma of the head of the pancreas with obstruction of the common duct for four weeks. There was postoperative stricture of the common duct. Postmortem section of the liver showed a moderate degree of portal cirrhosis.

Case 10.—Carcinoma of the pancreas had completely infiltrated the gland and obstructed the common duct. After operation ascending cholangitis developed and terminated in multiple abscesses of the liver. The liver weighed 1,780 Gm. Prothrombin response to vitamin K was rapid before operation.

Case 11.—Cholecystogastrostomy was performed for obstructive symptoms caused by carcinoma of the head of the pancreas. The liver showed a slight increase in fibrous tissue and round cell infiltration in the periportal areas.

Case 15.—The patient had carcinoma of the ampulla of Vater and died with extension of the tumor into the pancreas and the hepatic ligament and with obstruc-

Table 2.—*Poor Prothrombin Response to Vitamin K of Patients with Advanced Liver Disease*

Case	Diagnosis	Prothrombin (Per Cent) Initial	24 Hr. After Treatment	72 Hr. After Treatment	Daily Dose of Vitamin K (Mg.)	Comments
1	Cirrhosis	48	48	48	8*	Icterus
2	Cirrhosis	23	25	29	8*	Marked icterus; died on seventh day; diagnosis confirmed at autopsy
3	Cirrhosis	22	22	20	8*	Marked icterus; died on eighth day
4	Cirrhosis	35	33	30	8*	Slight icterus; died on fifteenth day
5	Cirrhosis	43	37	53	8*	Marked icterus; died on twenty-third day
6	Cirrhosis	58	63	60	8*	Icterus
7	Cirrhosis	58	60	65	8*	Icterus and ascites
8	Cirrhosis	80	82	85	8*	Icterus and ascites
9	Cirrhosis	65	60	57	8*	Icterus and ascites
10	Cirrhosis	65	68	64	8*	Icterus and ascites
11	Cirrhosis	52	52	57	10†	.....
12	Cirrhosis	78	..	75	10†	Clinically worse
13	Cirrhosis	75	80	93	10†	Ascites; no icterus
14	Cirrhosis	70	70	72	10†	Ascites; no icterus
15	Cirrhosis	40	43	48	10†	Ascites; no icterus
16	Cirrhosis	80	80	83	10†	Ascites; no icterus
17	Cirrhosis	80	80	80	10†	Ascites; no icterus
18	Banti's syndrome	81	83	95	8*	No icterus
19	Banti's syndrome	75	78	80	8*	No icterus
20	Banti's syndrome	64	60	56	8*	No icterus; died on the twenty-first day
21	Wilson's disease	78	64	61	8*	No icterus
22	Fatty infiltration with peritonitis	46	43	48	8*	Slight icterus; died on the thirty-third day
23	Multiple liver abscesses	57	56	54	8*	Marked icterus; died on the seventh day
24	Acute hepatitis	10	15	..	8*	Marked icterus; hemorrhagic diathesis; died on the fourth day
25	Acute hepatitis	48	34	50	8*	Marked icterus; died on the seventh day
26	Acute hepatitis	41	68	95	8*	Marked icterus
27	Metastatic carcinoma to the liver	57	62	100	8*	No icterus
28	Multiple liver abscesses	56	62	75	8*	Icterus
29	Multiple myeloma with large liver	62	62	61	8*	Liver 10 cm. below the costal margin
30	Banti's syndrome	64	66	75	8*	.....
31	Liver abscesses	75	68	60	8*	Died; multiple liver abscesses

* Patient was given 2-methyl-1, 4-naphthoquinone.

† Patient was given tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester.

tion of the common duct. Marked jaundice was present. The liver weighed 2,050 Gm. Histologic studies showed marked dilatation of biliary canaliculi, focal necrosis and cellular increase in triads.

Case 25.—The patient was jaundiced during the course of the illness owing to carcinoma of the cystic duct involving the common duct. Autopsy disclosed that

the liver was bile stained and weighed 2,250 Gm. Section showed round cell infiltration, a moderate amount of fibrosis and marked dilatation of biliary canaliculi.

Ten Patients with Jaundice Due to Hepatic Disease; Sections of the Liver Were Made Either at Operation or at Autopsy (tables 2 and 3).

CASE 1.—Biopsy of the liver disclosed extensive fatty infiltration of the parenchyma.

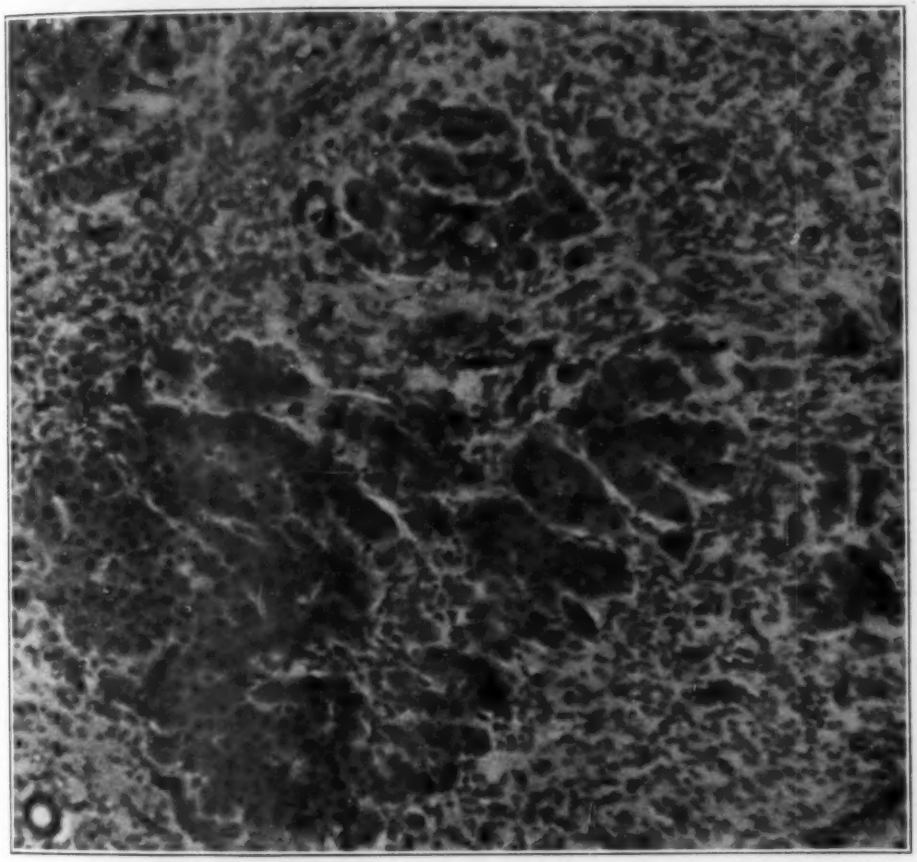

Fig. 3 (case 2, table 2).—Photomicrograph of the liver of a patient with extensive cirrhosis in whom vitamin K exerted no effect on prothrombin deficiency.

CASE 4.—At autopsy the liver weighed 1,470 Gm., showing changes of chronic passive congestion. Histologically, not much damage was seen. There was marked evidence of chronic passive congestion.

CASE 5.—The patient showed minimal icterus. Autopsy was done. The liver weighed 1,500 Gm. Sections showed slight periportal fibrosis. The intrahepatic ducts were not dilated.

CASE 7.—The patient had been jaundiced one year and had had ascites for three of four months. Autopsy disclosed advanced portal cirrhosis. All sections showed marked fibrosis with evidence of regeneration.

CASE 19.—The patient had Banti's syndrome and ascites. The liver weighed 1,910 Gm. and had a granular surface; the cut surface showed marked perilobular fibrosis. Histologic study showed moderate portal cirrhosis and extensive areas of recent and old necrosis.

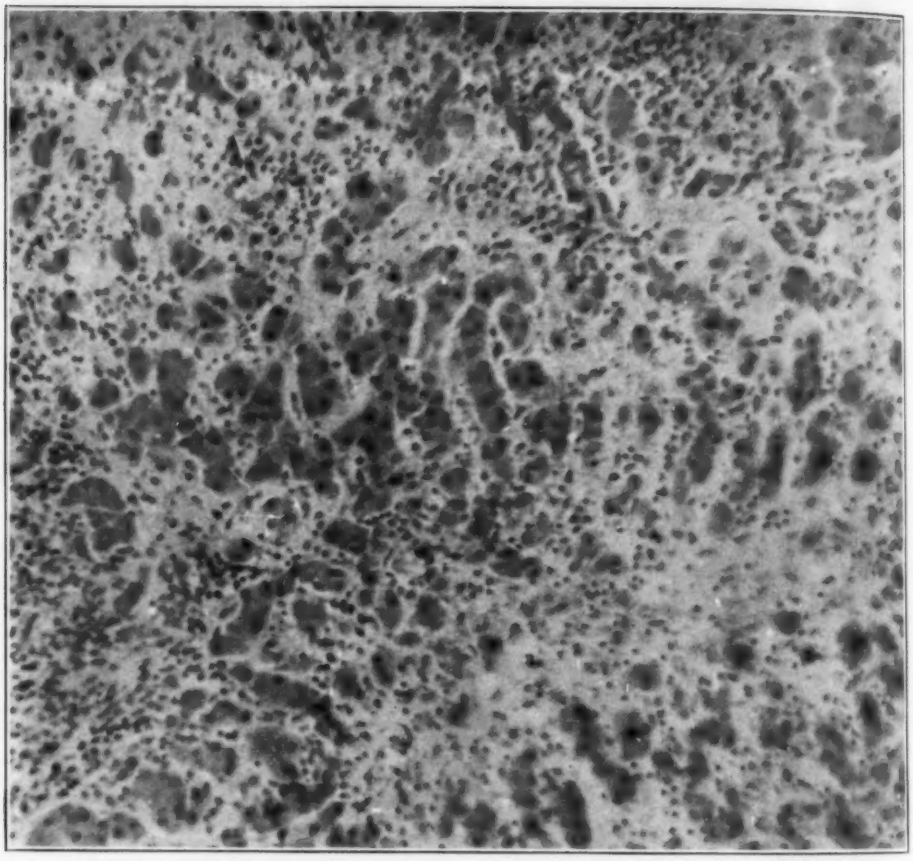

Fig. 4 (case 5, table 2).—Photomicrograph of the liver of a patient with extensive cirrhosis in whom vitamin K exerted no effect on prothrombin deficiency.

CASE 22.—Biopsy of the liver disclosed extensive parenchymatous degeneration. The liver was small.

CASE 23.—The patient died with multiple interstitial liver abscesses following drainage of the common duct (choledocholithiasis). At autopsy the liver weighed 2,200 Gm. and was purple-bronze in color. Section showed moderate fatty degeneration, early fibrosis of biliary distribution and marked round cell infiltration about the triads.

CASE 28.—In this case there were multiple liver abscesses, localized peritoneal abscesses and subdiaphragmatic abscess following rupture of the gallbladder due to carcinoma of the head of the pancreas. The obstruction was found to be incomplete at autopsy. The liver showed multiple small abscesses.

CASE 31.—The patient died of multiple liver abscesses following appendectomy complicated by septic thrombophlebitis. Ascites developed before death. The liver weighed 3,300 Gm. and was extensively destroyed by abscesses and intervening necrosis of the parenchyma.

CASE 1 (table 3).—The patient had a history of alcoholism, and biopsy of the liver revealed fatty infiltration of the parenchyma and some hyalinization.

TABLE 3.—*Patients with Clinical Evidence of Liver Damage and Prothrombin Deficiency Who Have Received Vitamin K Continuously*

		Prothrombin (Per Cent)						
		Initial	Subsequent Determination					
Case	Diagnosis	Determination						Comment
1	Cirrhosis	52	60 (5 weeks)	63 (8 weeks)	78 (12 weeks)		100 (56 weeks)	Gradual clinical improvement; paracenteses became unnecessary
2	Cirrhosis	55	72 (3 weeks)	100 (8 weeks)			100 (59 weeks)	Clinically excellent on medical regimen; no ascites for 6 mo.
3	Cirrhosis	74	55 (3 weeks)	60 (6 weeks)	58 (8 weeks)	45 (25 weeks)	63 (19 weeks)	Still unimproved; continued to require abdominal paracenteses weekly; died at end of 6 mo.
4	Cirrhosis	70	75 (3 weeks)	55 (5 weeks)	37 (7 weeks)			Died at end of 2 mo.; subcutaneous ecchymoses

COMMENT

The patients whose cases are presented here were divided into three groups according to causation of the prothrombin deficiency. In all cases the therapeutic tests given with vitamin K were the same. These tests consisted either of oral administration of 8 mg. of 2-methyl-1, 4-naphthoquinone (menadione) with 2.5 Gm. of bile salts per day or of intravenous injection of 10 mg. of the water-soluble compound tetrasodium 2-methyl-1, 4-naphthoquinone diphosphoric acid ester.[10] The prothrombin activity was determined at the end of twenty-four hours by the serial dilution one stage technic.[4c] The first group (table 1) consisted of 21 patients with obstructive jaundice, 4 with complete external biliary fistula, 2 with esophageal carcinoma and 1 with gastric ulcer under treatment; the last-named 3 had inadequate food intake, and all had prothrombin deficiency. The second group consisted of 31 patients with prothrombin deficiency and jaundice due to intrahepatic disease. The third group was composed of 4 patients without jaundice who presented primary prothrombin deficiency associated with cirrhosis of the liver and ascites.

10. The compound used was synkovite-Roche.

Specimens of the liver were obtained in a number of the cases in each group at autopsy or at laparotomy. The histologic data are reported in the accompanying protocols. Photomicrographs of 4 of the specimens are presented (figs. 1, 2, 3 and 4).

In the cases shown in table 1 there was one common factor—the inadequate absorption of vitamin K. The factor responsible for this inadequate absorption was: (1) absence of bile salts from the intestine in 21 cases of obstructive jaundice of proved causation and in 4 cases of complete external biliary fistula or (2) inadequate ingestion of foods containing vitamin K in 3 cases. It was characteristic of the cases in this group that the administration of vitamin K by a method providing certain absorption caused an immediate elevation in the plasma prothrombin level. These were consecutive cases of obstructive jaundice observed at the University of Chicago Clinics, and in none did the response to vitamin K fail to occur.

The second group included 17 patients with cirrhosis of the liver and jaundice, 4 with the so-called Banti syndrome and mild jaundice, 5 with extensive destruction of the liver due to abscesses and 3 with acute hepatitis or catarrhal jaundice. The characteristic of this entire group was that the depressed plasma prothrombin was either not affected or only slowly elevated by the administration of vitamin K. As contrasted with the first group, the common factor here was primary liver disease of varied causation associated with jaundice.

Our previous report of a smaller but similar series of cases indicated that the plasma prothrombin determination in relation to a therapeutic trial with vitamin K provides a reliable differentiation between intrahepatic and obstructive jaundice.[4d] The present, more extensive series confirmed the earlier observations. Although a certain amount of liver damage usually accompanies obstructive jaundice even of a short duration, we have not yet encountered a case in which this damage was sufficient to prevent the prompt response of prothrombin to therapy with vitamin K. However, such cases will undoubtedly occur when untreated obstruction has produced sufficient liver damage, i. e. biliary cirrhosis. In such a case, the failure of prothrombin to respond to a therapeutic test would lead to an erroneous diagnosis of primary intrahepatic disease and obscure the basic pathologic condition itself, possibly amenable to operation. In this regard it is of interest that 1 of our patients had postoperative stricture of the common duct with jaundice of six months' duration and showed severe liver damage at autopsy but nevertheless displayed a rapid response to therapeutic test (case 3).[11]

11. We recently observed a 55 year old patient on whom cholecystectomy was performed for cholelithiasis in January 1941 and who became icteric in April 1942. Intermittent chills and fever continued, and by June 1942 ascites had developed. This patient, when seen in this clinic, had an icteric index of 42 units and a prothrombin level of 50 per cent. In spite of adequate vitamin K therapy the patient's prothrombin had risen to only 68 per cent after one week's treatment. At operation

The question arises: Is it possible to anticipate the extent of the liver damage from the response to vitamin K in a given patient with liver disease? In this regard we have examined the microscopic pathologic picture present in the liver in 17 cases in both groups (cases of tables 1 and 2). Brief descriptions of the microscopic pathologic picture of the liver in 6 cases of group 1 and 11 of group 2 have been presented. No correlation was observed between the degree of damage shown in the microscopic sections or in the gross appearance of the liver and the initial prothrombin level or the rate and degree of prothrombin response. These observations led us to conclude that the degree of prothrombin deficiency with liver disease does not reflect the extent of the injury to the liver and that in this sense prothrombin deficiency is not a reliable measure of liver function. Moreover, we have observed patients with demonstrable primary liver disease in whom the plasma prothrombin was found to be normal.

However, in 4 cases presented in table 3 the prothrombin level under continuous adequate vitamin K intake seemed to reflect the clinical course of the disease in the individual patient. Two of the patients (cases 1 and 2) with hepatic cirrhosis and ascites gradually improved on medical management, requiring less frequent paracenteses, and were finally able to resume normal activity. In these 2 patients the prothrombin level rose over a period of eight and twelve weeks from 52 and 55 per cent to normal. The other 2 patients showed the reverse, the level going from 74 and 70 per cent to 45 and 32 per cent; both finally died of cirrhosis. Sections of the liver were obtained from all 4 patients of this group. Though few in number, these patients provided a strong suggestion that the prothrombin level (always supposing an adequate intake of vitamin K) provides a good index to the course of the disease for that particular patient.

CONCLUSIONS

The prothrombin determination in connection with a therapeutic trial of vitamin K therapy constitutes an accurate means of differentiation between intrahepatic and extrahepatic jaundice.

The prothrombin determination with or without trial vitamin therapy is not qualified as a quantitative test of liver function.

Serial prothrombin determinations over a period of time on a patient with hepatic disease may be a suitable index of the progress of the disease.

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two large stones were found in the common duct. A specimen of the liver was taken for biopsy, and Bacillus typhosus was cultured from it. Histologically, marked inflammatory changes were found in the periportal areas with an increase in the fibrous tissue.

This case serves to demonstrate the simultaneous occurrence of extensive liver disease and obstruction to the common duct in the same patient. In such cases diagnosis cannot be made by the prothrombin response to vitamin K.

BENIGN TUMORS OF THE STOMACH

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LAURENCE MISCALL, M.D.

AND

STANLEY F. MORSE, M.D.

NEW YORK

Benign gastric tumors have received rather minor consideration in the literature compared to that accorded to ulcer and malignant lesions. Although sufficient reasons certainly justify this, several facts seem to warrant more than a mere academic acknowledgment of the benign

TABLE 1.—*Tumors of the Stomach Observed at Autopsy* *

Malignant		Benign	
Adenocarcinoma	81	Polyp	14
Scirrhous carcinoma	12	Fibroma	8
Medullary carcinoma	8	Papilloma	4
Colloid	4	Leiomyoma	2
Carcinoma simplex	4	Fibromyoma	2
Linitis plastica	2	Adenoma	2
Krukenberg	2		
Total malignant tumors	113 (78%)	Total benign tumors	32 (22%)
Total tumors of the stomach			145
Number of autopsies, 1930 to 1934 inclusive			4,413
Autopsies at which stomach tumors were observed			3.28%
Autopsies at which malignant stomach tumors were observed			2.56%
Autopsies at which benign stomach tumors were observed			0.72%

* Autopsies done at Bellevue Hospital, 1930-1934 inclusive.

tumors. These facts may be briefly enumerated: 1. The reported clinical rarity is certainly relative and due in part to lack of recognition. 2. Errors in diagnosis have too commonly led to ill timed and unnecessarily radical operations. 3. Critical illness frequently results from not unusual strangulation, pyloric obstruction or hemorrhage. 4. Malignant degeneration of certain types occurs rather often. Since these facts, variously emphasized by others, have been encountered in our own experience, it seems advisable to report this review of the situation at Bellevue Hospital, New York.

Various authors have differed widely in estimating the relative frequency of benign and malignant gastric neoplasms. The rather sharp contrast between the figures obtained from autopsies and those obtained from clinical examinations in this study clearly illustrates one basis for such diversity of opinion.

In 4,413 autopsies done at Bellevue Hospital during five years (1930-1934), 22 per cent of all gastric tumors observed were benign (table 1).

This figure closely approximates the 22.8 per cent in the 11,000 autopsies of Stewart [1] at Leeds, England, and the 26.2 per cent of Rigler and Ericksen [2] in 6,242 autopsies at the University of Minnesota (table 3).

Comparison of the records of 76,077 adult surgical and medical patients admitted to the hospital during three years and seven months (Jan. 1, 1935, to Aug. 1, 1938) revealed that 456 had been operated on for gastric tumors. In 450 of the cases the neoplasms were malignant, and in 6 they were benign. Thus 1.3 per cent of all gastric tumors with symptoms or signs sufficient to warrant operation were benign (table 2).

TABLE 2.—*Tumors of the Stomach Among Patients Admitted to the Hospital* *

Total patients admitted (adult, medical and surgical)	76,077
Total malignant gastric tumors	450 (98.7%)
Total benign gastric tumors	6 (1.3%)
Adenoma	4
Fibromyoma	1
Leiomyoma	1

* Patients admitted to Bellevue Hospital, Jan. 1, 1935, to Aug. 1, 1938. Of the patients admitted, 0.6 per cent had gastric tumors treated.

TABLE 3.—*Frequency of Benign Tumors Reported in the Literature*

Author	Material	Benign Tumors	Malignant Tumors	Ratio	Gastric Tumors, per Cent
Stewart [1]	11,000 autopsies	78	263*	3.3:1	22.8
Rigler and Ericksen [2]	6,242 autopsies	49	138	2.8:1	26.2
				(operative cases)	(operative cases)
Eusterman and Senty [3]	2,195 operative cases	27	2,168	78:1	1.3
	2,285 inoperative cases	..	4,480	165:1 (total)	
Dudley, Miscall and Morse	4,413 autopsies †	32	113	3.5:1	22.0
	456 operative cases ‡	6	450	75:1	1.3
					(operative cases)

* Carcinomas.
† See table 1.
‡ See table 2.

This operative incidence checks exactly with that in the larger group reported by Eusterman and Senty [3] (table 3).

At least part of the disparity between the figures obtained from autopsies and those obtained from clinical observations arises from the fact that only the symptomatic benign tumors come to operation. The majority of benign tumors may give few or no symptoms and may be

1. Stewart, M. J.: Observations on the Relation of Malignant Diseases to Benign Tumors of the Intestinal Tract, Brit. M. J. **2**:567-569, 1929.

2. Rigler, L. G., and Ericksen, L. G.: Benign Tumors of the Stomach, Radiology **26**:6-15, 1936.

3. Eusterman, G. B., and Senty, E. G.: Benign Tumors of the Stomach, Surg., Gynec. & Obst. **34**:5-15, 1922.

completely overlooked during life. However, the general estimate that 0.5 to 5 per cent of all gastric tumors are benign is apparently too low. The figure is probably nearer 15 to 20 per cent. An interesting observation reported in the literature was that of Rieniets [4] at the Mayo Clinic. His diligent examination for only gastric leiomyomas in 200 consecutive autopsies revealed that there were such benign tumors in 16 per cent, frequently small and asymptomatic but still definite, and that malignant disease was present in 6 per cent.

At Bellevue Hospital the records of 76 microscopically examined benign gastric tumors have been collected from 21,026 cases in which autopsy was done in twenty-three years (June 1, 1915 to June 1, 1938) for all causes of death. The details of these cases recorded in tables 4 and 5 have been correlated with the reports of other authors. The variations apparent here were attributed previously by others to the lack of both or either complete microscopic diagnosis and uniform terminology among pathologists. This conclusion is warranted by our experience. However, in all reports mucosal polyps, papillomas and myomas constitute a real majority. Apparently the pylorus is more selectively involved, but no type of tumor displays any distinct predilection for any one portion of the stomach.

Sixty of the 76 patients had been observed sufficiently in the hospital for a complete clinical diagnosis to be made. Despite this, in not one case was the correct diagnosis made before death. Careful review of these 60 satisfactory records shows many interesting facts. Forty-two (70 per cent) of the 60 patients adequately followed were quiescent and asymptomatic. In addition, physical examination and laboratory work-up including roentgen studies were devoid of any positive findings indicative of gastric disease. All types occurred asymptomatically throughout the stomach. Although clinical diagnoses covered a multiplicity of possibilities, the chief complaint was not referable to the stomach in any 1 of these 42 cases. Most patients had other causes substantiated by postmortem examination for any gastrointestinal symptoms. Furthermore, close check-up of postmortem reports failed to reveal evidence that these tumors might have been symptomatic during life, since gastritis, strangulation, ulceration, bleeding and obstructive prolapse were all absent.

In the light of this experience with 42 proved benign gastric tumors it is reasonable to state that these tumors frequently may remain asymptomatic for years without detriment to the person.

Such favorable conditions do not always prevail. Quiescence may be supplanted by activity with vague and atypical symptoms leading to confusion rather than clarity. This situation existed in the other 18 suffici-

4. Rieniets, J. H.: The Frequency and Pathologic Aspects of Gastric Leiomyoma, Proc. Staff Meet., Mayo Clin. **5**:364-366, 1930.

TABLE 4.—*Correlation of Types of Benign Gastric Tumors Observed at Bellevue Hospital with Those Reported in the Literature*

Authors	Cases	Polyp				Myoma		Fibroma		Adenoma		Angioma		Dermoids and Cysts		Lipoma		Other Tumors	
		Single		Multiple															
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Bellevue Hospital *	70†	23	30.2	16	21.0	15§	20.0	12	15.80	8	10.5	..	....	..	...	..	....	2¶	2.6
Eusterman and Senty [3]	27‡	3	11.1	1	3.7	10	37.3	5	18.60	2	7.3	4	14.7	2	7.30				
Judd, E. S., and Hoerner, M. T.: Am. J. Surg. **31**: 427-430, 1936	50‡	——— Excluded ———				35	70.0	8	16.00	3	6.0	3	6.0	Excluded		1	2.0		
Balfour, D. C., and Henderson, E. F.: Ann. Surg. **85**: 354-359, 1927	58‡	14	24.1	4	6.8	23	39.6	..	....	4	6.8	4	6.8	3	5.10	..	....	6	10.3
Rigler and Ericksen [2]	49†	———	31	63.0 ———		12	24.5	..	....	2	4.0	..	....	..	....	..	....	4	8.5
Stewart [1]	78†	27	34.5	20	25.6	22	28.2	..	....	..	....	..	....	..	....	5	6.4	4#	5.3
Ellason, E. L., and Wright, V. W. M.: Surg., Gynec. & Obst. **41**: 461-472, 1925	560 (collected)	77	13.6	11	1.9	321	57.3	23	4.12	31	5.5	10	1.7	29	5.17	28	5.0	30	6.7
	50 (personal)§	32	64.0	1	2.0	4	8.0	6	12.00	5	10.0	..	....	1	2.00	1	2.0		
Minnes, J. F., and Geschickter, C. F.: Am. J. Cancer **28**: 130-149, 1936	931 (collected)	271	29.0	16	1.7	344	37.0	42	4.50	42	4.5	15	1.6	38	4.10	32	3.4	130	14.2
	50 (personal)	5	10.0	26	52.0	16	32.0	1	2.00	..	....	1	2.0	..	....	..	....	1	2.0
Percentage limits		——— 14.8 to 66.0 ———				8.0 to 57.3		2.0 to 18.0		4.5 to 10.0		1.6 to 14.7		2.0 to 7.3		2.0 to 6.4			

* A total of 21,026 autopsies were done at Bellevue Hospital between June 1, 1915, and June 1, 1938; the 76 cases in which benign tumors were observed represent 0.36 per cent of the autopsies.

† Tumors observed at autopsy.

‡ Tumors observed at operation.

§ Tumors observed at operation and autopsy.

‖ Leiomyoma, 4; fibroleiomyoma, 1; fibromyoma, 5; multiple myoma, 1; solitary myoma, 4.

¶ Fibroadenoma, 1; fibrolipoma, 1.

Among 5,700 autopsies.

ently observed cases. In these cases the symptoms, the physical signs and the laboratory and roentgen studies failed to agree sufficiently to indicate the gastric lesion clearly. The benign tumors were not even mentioned in these cases, all being either incorrectly diagnosed or missed completely. Reasons for this evident confusion will be presented later in consideration of the operative cases.

The association of ulceration, gastritis and malignant disease with benign gastric tumors has easily recognized importance. In various series the following figures were reported: Ulceration either in the

TABLE 5.—*Distribution of Various Types of Benign Gastric Tumors Observed at Bellevue Hospital*

Location	Polyp	Myoma	Fibroma	Adenoma	Total	Percentage
Pylorus	15	6	2	6	29	47*
Media	14	7	3	1	25	39†
Cardia	4	2	3	1	10	14‡
Diffuse	6	0	4	0	10	
Unstated	0	1	0	1	2	
Total	39	16	12	9	76	

* The percentage reported by E. S. Judd and M. T. Hoerner (Am. J. Surg. **31**: 427-430, 1936) was 66; that reported by J. F. Minnes and C. F. Geschickter (Am. J. Cancer **28**: 130-149, 1936) was 46.

† The percentage reported by Judd and Hoerner was 24; that reported by Minnes and Geschickter was likewise 24.

‡ The percentage reported by Judd and Hoerner was 10; that reported by Minnes and Gescheckter was 30.

TABLE 6.—*Distribution of Asymptomatic Benign Tumors in Forty-Two Cases*

Location	Polyp	Fibroma	Myoma	Adenoma	Fibrolipoma	Total
Pylorus	8	2	0	2	0	12
Media	4	0	0	0	0	4
Cardia	4	2	2	0	0	8
Unstated	2	2	1	0	1	6
Multiple	8	1	0	0	0	9
Subserosal	0	1	2	0	0	3
Total	26	8	5	2	1	42

tumor or elsewhere in the stomach and the duodenum occurred in 15 to 46 per cent of the cases. Malignant degeneration had an incidence of about 25 per cent in the mucous polyps. Gastritis of all degrees has been repeatedly observed but frequently overlooked in pathologic reports unless of a severe grade. It is likely that many benign tumors remain asymptomatic until the onset of one or all of these complications. Table 7 details our figures in comparison with those of other series we have collected.

Ulcers of the stomach or the duodenum coexisted with benign gastric tumors in 11 cases, 3 of which may be cited: In case 39 there was fibromyoma at the cardia with multiple bleeding duodenal ulcers. In

case 15 there were multiple polyps of the fundus with acute gastric ulcers in this region. In case 46 there was ulcerated pyloric fibromyoma with acute gastric and duodenal ulcers, marked gastritis and massive hemorrhage.

The following short summaries of 3 cases of gastric carcinoma existing in benign tumors are of interest:

In case 33 the patient showed minimal gastric symptoms but had two gastric polyps in the pars media. A pedunculated tumor was

TABLE 7.—*Association of Ulcer and Malignant Disease with Benign Gastric Tumors in This Series and Various Series Reported in the Literature*

Authors	Cases	Ulcer		Associated Malignant Growth		Malignant Degeneration		Comment
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	
Benedict, E. B., and Allen, A. W.: Surg., Gynec. & Obst. **58**: 79-84, 1934	17	..	....	..	....	7	41.2	Specimens were obtained at operation in cases of polyp with fairly severe symptoms
Stewart[1]	47	..	....	..	....	13	27.6	Polyps observed at autopsy
Miller, T. G.; Eliason, E. L., and Wright, V. M. W.: Arch. Int. Med. **46**: 841 (Nov.) 1930	23	..	....	..	....	8	35.0	Polyps examined
Minnes, J. F., and Geschickter, C. F.: Am. J. Cancer **28**: 130-149, 1936	31	..	....	..	....	3	10.0	Polyps examined
Mills, G. P.: Brit. J. Surg. **10**: 226-231, 1922	20	..	....	..	....	4	20.0	Polyps
Brunn, H., and Pearl, F.: Surg., Gynec. & Obst. **43**: 559-598, 1926	84	..	....	..	....	10	12.0	Collected cases of polyposis
Judd, E. S., and Hoerner, M. T.: Am. J. Surg. **31**: 427-430, 1936	50	..	46.0					
Balfour, D. C., and Henderson, E. F.: Ann. Surg. **85**: 354-359, 1927	58	..	17.0					
Dudley, Miscall and Morse, present report	76	11	15.8	2	2.6	10	13.0	Autopsy done in all cases
	39	..	....	..	....	9	23.0	Polyps observed at autopsy

reported as a simple mucous polyp, while the other, which was of the sessile type, showed definite carcinomatous degeneration with metastases to the mediastinal and regional lymph nodes.

In case 21 the patient with symptoms and signs sufficient for a clinical diagnosis of carcinoma had two distinct papillary adenomas at the pylorus. The sessile tumor, however, showed adenocarcinomatous degeneration with scattered peritoneal metastases.

In case 50 marked symptoms referable to the stomach showed a somewhat sessile pyloric papilloma with carcinomatous degeneration and metastases in the liver.

All 3 patients showed ulceration of the malignantly degenerating benign tumor but only in the more sessile tumors. Most important was the fact that in these 3 cases the condition progressed to the stage of metastatic malignant disease before any of the patients were forced into the hospital by gastric symptoms.

Two other cases merit citation: In case 7 the patient had a pedunculated polyp in the pars media with a large carcinoma of the greater curvature. In case 9 the patient had a pyloric mucous polyp associated with a papillary adenocarcinoma at the cardia on the lesser curvature. In neither of these cases was malignant degeneration of a benign tumor represented; rather the coexistence of benign and malignant lesions in the same stomach was shown.

Benign gastric tumors were associated with extragastric malignant lesions on only 3 occasions. In case 10 there was gastric leiomyoma with retroperitoneal fibrosarcoma. In case 45 there was gastric papilloma with prostatic adenocarcinoma. In case 65 there was gastric myoma with primary carcinoma of the liver.

Benign gastric tumors were associated with extragastric benign lesions only twice. In case 34 there was gastric polyp with sigmoidal polyp. In case 20 there were multiple fibromas of the stomach with a polyp in the ascending colon.

The practical difficulties of detailed diagnosis in such cases are readily evident, but the possibility of such complex association should not be forgotten. This is especially important when these previously undiagnosed lesions first come to light at operation, for radical revision of surgical procedure may then become imperative. The possibility of progression to the stage of metastatic malignant disease with little or no change in symptoms must be constantly realized.

The operative benign tumors, 32 cases of which have been collected in ten years, may now be considered. Although many records are too incomplete to warrant detailed tabulation as in the cases in which autopsy was done, certain facts deserve emphasis as operative and clinical experience.

The bare 30 per cent of tumors correctly diagnosed before operation compares rather unfavorably with the 65 per cent found more or less by accident. In the latter group, 50 per cent were labeled gastric carcinoma, while the other 15 per cent were called bleeding ulcers almost exclusively. Unquestionably an error of such magnitude demands that its causes be searched out. If this situation in the presence of obvious symptoms cannot be remedied, certainly no success must be expected in the larger relatively asymptomatic group. Such a survey was made and yielded this one essential fact, that the mistakes have usually emanated from inadequate appreciation of the clinical and laboratory characteristics of these tumors. The experience of this study seems to justify listing some facts more or less characteristic of benign gastric tumors.

The large majority of patients coming for treatment give a history of some protracted gastric disturbance. Past complaints, usually mild and irregular, most often lack the periodicity, the progression and other common attributes of ulcer or carcinoma. The patient has more or less neglected these symptoms until driven to the hospital by one of the more severe complications of pyloric obstruction, hemorrhage or strangulation. Without doubt this sudden transition from fairly good health with few symptoms to acute illness with alarming symptoms has been rather characteristic in our experience.

Gastric hemorrhage (occurring in 40 per cent of all cases) was the commonest initial symptom forcing patients to seek treatment. It generally resembled the massive bleeding of ulcer more closely than the slow weeping of carcinoma. Loss of blood was sudden and extensive enough in half of these cases to cause surgical shock with the hemoglobin content below 50 per cent. Such severe exsanguination occurred almost exclusively in patients with mucous polyps and more in persons with pedunculated than in those with sessile tumors. A few patients exhibited anemia with weakness secondary to slower bleeding. In only 4 of 12 cases was the correct diagnosis made, but proper attention to the antecedent history might well have increased this figure. Two of these patients died.

Pyloric obstruction was present in 10 cases, representing an incidence of about 30 per cent. It was either progressive or intermittent in character, dependent on the location and the type of tumor.

The sessile pyloric tumors accompanied by pylorospasm frequently produced persistent and progressive symptoms of obstruction. A roentgen filling defect with gastric residue was not unusual. In this they closely simulated carcinoma, even though, being small and intramural, they did not bleed or ulcerate as frequently.

The pedunculated and mobile benign tumors distant from the pylorus presented a contrasting picture. Symptoms of obstruction were definitely intermittent with attacks of nausea and vomiting being precipitated by prolapse to or through the pyloric ring. These bouts abated or ceased with recession of the tumor from the gastric outlet. (One patient with a pedunculated polyp had no symptoms while he was in the reclining position but complained of nausea and vomiting after meals in the erect position.) Roentgenograms varied. Gastric residue was reported only in the presence of prolapse. The filling defect was often replaced by bizarre regular circling of the mass by barium sulfate in either the duodenum or the stomach. Subsequent studies frequently showed nothing, particularly in an asymptomatic period after return of the tumor to its normally higher position.

In review, the findings of roentgen studies in cases of both the pedunculated and the sessile benign tumors may closely resemble the

findings in cases of carcinoma. The sessile tumors at the pylorus may persist in showing such features. The pedunculated ones, however, frequently may change to an essentially normal picture with retreat of the tumor from the gastric outlet. Clinical symptoms usually follow a like pattern. Such findings have been emphasized by roentgenologists many times. It remains for the surgeon to supplement such reports with his clinical examination in order to more commonly make the diagnosis.

Strangulation may be a serious complication of these tumors, but since we have not observed it personally, we can add nothing to the present literature from this study.

Gastritis of varying degree has frequently been observed. It is probably more common than suspected and may account for many of the low grade symptoms in the relatively asymptomatic cases.

As previously stated, in 13.1 per cent of all the cases in which autopsy was performed there was malignant degeneration, polyps being present in 9 of the 10 cases. Thus of the 39 polyps autopsied 9 (23 per cent) showed malignant changes. In the last 16 operative and microscopically diagnosed benign gastric tumors, 3, or 19.2 per cent, had similar pathologic changes, limited exclusively to such mucous polyps. Such high figures are generally recognized and should not be overlooked in considering methods of treatment (table 7).

The following cases are briefly reported to illustrate some of the points considered significant in the clinical course of these benign tumors.

REPORT OF CASES

Case 1 (Fibromyoma).—F. C., a 57 year old white man, was admitted on Feb. 2, 1935, with a ten year history of irregular epigastric pain, nausea and vomiting. Diet and the giving of alkalis had produced little relief. All symptoms had progressed in the last three years. He had lost weight but had never had bloody stools or vomitus. Except for loss of weight the physical examination showed little. Six months previously roentgen studies had shown annular constriction with defective filling of the prepyloric area with gastric retention. A diagnosis of carcinoma of the stomach and arrested pulmonary tuberculosis was made.

Operation was done on February 12. A walnut-sized, freely movable mass in the stomach on the lesser curvature just proximal to the pyloric ring was removed by gastric resection with posterior Polya anastomosis. Signs of consolidation of both lower lobes developed on the twenty-sixth postoperative day, and the patient died. Postmortem examination showed tuberculous pneumonia.

Gross Pathologic Examination.—There was a firm tumor mass just proximal to the pylorus on the lesser curvature of the stomach. There was some hypertrophy of the pylorus.

Microscopic Examination.—This tumor was made up of smooth muscle with a moderate amount of fibrous tissue throughout.

Pathologic Diagnosis.—The pathologic diagnosis was fibromyoma.

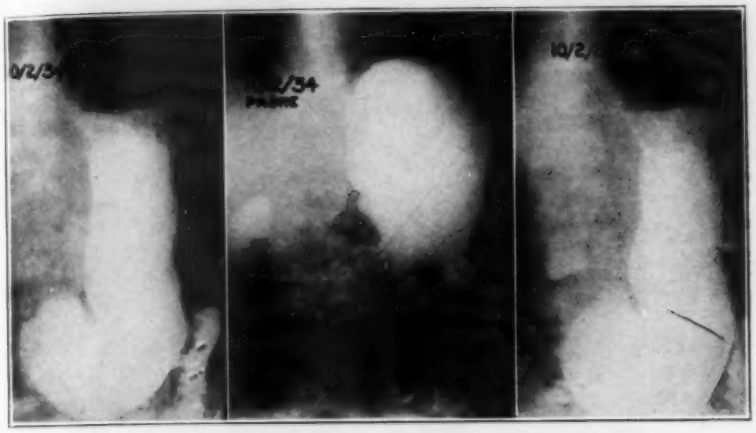

Fig. 1 (case 1).—Preoperative gastric roentgenograms of a dilated stomach with a prepyloric defect interpreted as malignant disease.

Fig. 2 (case 1).—Photomicrograph of a specimen described as fibromyoma.

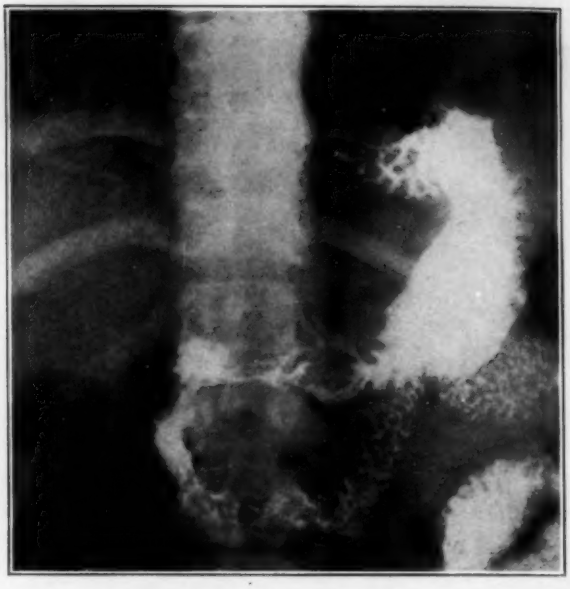

Fig. 3 (case 2).—Preoperative gastric roentgenogram showing a circumscribed translucent area in the prepyloric region the size of a walnut which was interpreted as being a benign tumor.

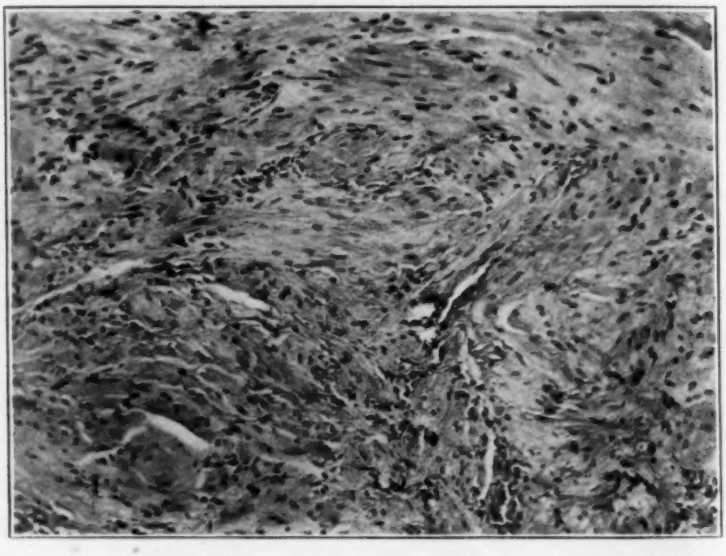

Fig. 4 (case 2).—High power photomicrograph of a tumor excised locally from the pylorus and reported as a fibroleiomyoma.

This patient had a benign intramural tumor at the pylorus causing long-standing symptoms of obstruction. Gastric resection was unnecessarily carried out and may have contributed to the lighting-up of the old tuberculosis.

CASE 2 (Fibroleiomyoma).—J. D., a 50 year old white man, was admitted to the hospital Feb. 16, 1940. His illness began thirteen months previously with emesis of about 1½ cups (177 cc.) of bright red blood. Shortly thereafter he had tarry stools, became weak and spent nineteen days in the hospital. After that symptoms of nausea, vomiting and loss of weight steadily progressed with little relief from alkaline powders and diet. Two weeks before admission less severe hematemesis recurred. Physical examination showed a somewhat emaciated white man without other significant findings. All laboratory work fell within normal limits. Roentgenograms on February 19 showed a walnut-sized, translucent, circumscribed area in the prepyloric region of the stomach interpreted as a benign tumor.

Operation was done on February 21. A small intramural mass was locally excised. The patient made an uneventful recovery, being discharged on his twenty-third postoperative day.

Gross Pathologic Examination.—Macroscopic examination showed the specimen to consist of an irregularly shaped piece of tissue about 1.5 by 0.5 by 0.5 cm. Its surface was uneven, and it was white and firm.

Microscopic Examination.—On section there was seen much muscle and fibrous tissue which ran in all directions. There was a slight attempt at whorl formation. There was no evidence of infection or malignancy. No mucosa was seen, which would identify the tissue definitely.

Pathologic Diagnosis.—The pathologic diagnosis was fibroleiomyoma.

Course.—The patient remained well for about one year, when there was recurrence of symptoms due to a small gastric ulcer. This was not found either on the first roentgen examination or at operation (figs. 3 and 4).

This patient was exactly similar to the patient in case 1 except that in his case obstruction was complicated by hemorrhage.

CASE 3 (Leiomyoma).—E. E., a 58 year old white woman, was admitted to the hospital Sept. 21, 1937, with rather sudden onset of dizziness and fainting spells. Four days before she had vomited a large amount of blood. She had had tarry stools for three days. Except for irregular indigestion, the rest of the history was not pertinent. The patient was in mild shock. The pulse rate was 120. The blood pressure was 140 systolic and 60 diastolic. The red blood cell count was 1,600,000. The hemoglobin content was 30 per cent. The stools and the vomitus both gave positive reaction for blood. Roentgen examination on October 18 was reported as showing no gastric retention with request for reexamination, but roentgen examination on October 29 was reported to show a persistent defect in the antral region of the stomach suggestive of a neoplasm.

Operation was done on November 10. A firm pedunculated mass the size of a golf ball attached to the posterior wall along the greater curvature and prolapsed to the pylorus was excised by gastrotomy. The patient had an uneventful postoperative course. At the time of writing she had been followed for four years and is in good condition without symptoms. A check series of gastric roentgenograms done on December 15 showed a normal stomach and duodenum.

Pathologic Diagnosis.—The pathologic diagnosis was leiomyoma (figs. 5 to 11).

Fig. 5 (case 3).—Preoperative gastric roentgenograms showing a dilated stomach with retention and persistent antral defect suggestive of new growth. Roentgenograms taken ten days previously failed to show any such changes.

Fig. 6 (case 3).—View of a tumor excised locally from the greater curvature near the pylorus of the stomach.

Fig. 7 (case 3).—View of the tumor in figure 6 showing ulceration.

Fig. 8 (case 3).—View of the tumor in figures 6 and 7 showing encapsulation.

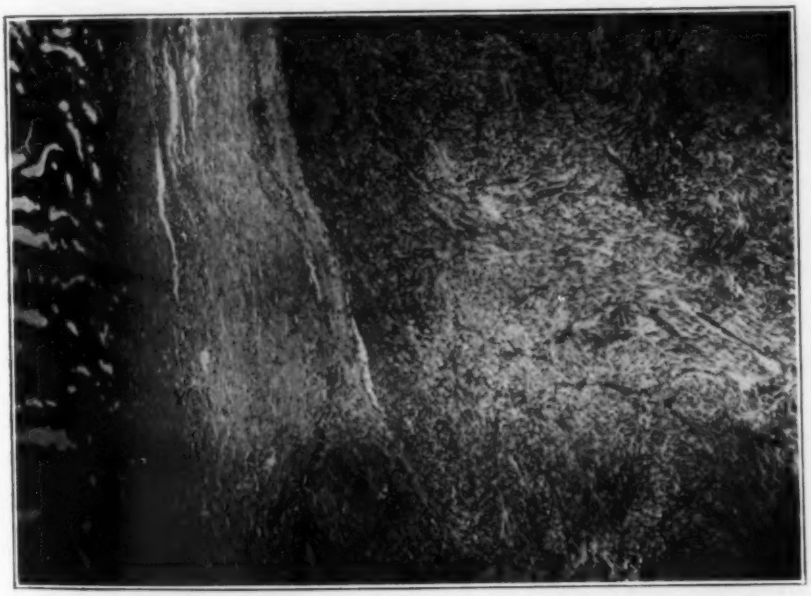

Fig. 9 (case 3).—Low power photomicrograph of a specimen reported as leiomyoma.

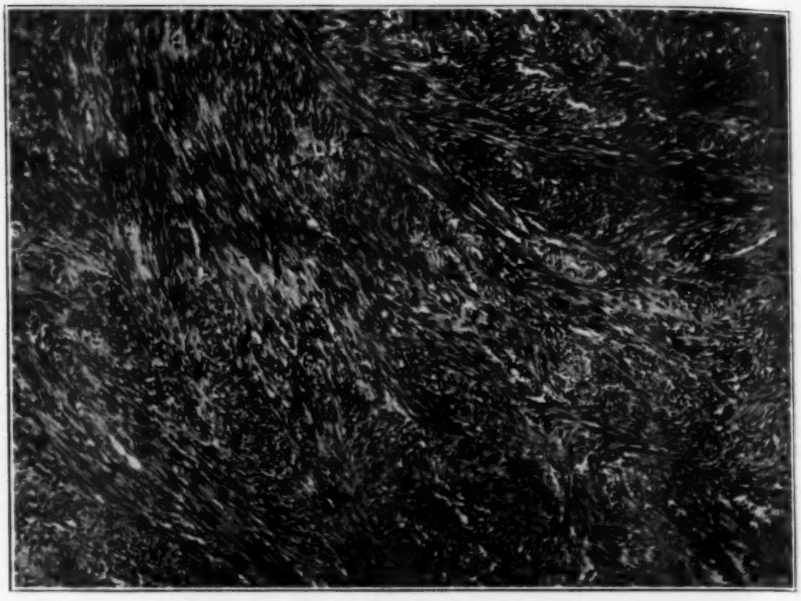

Fig. 10 (case 3).—High power photomicrograph of specimen shown in figure 9.

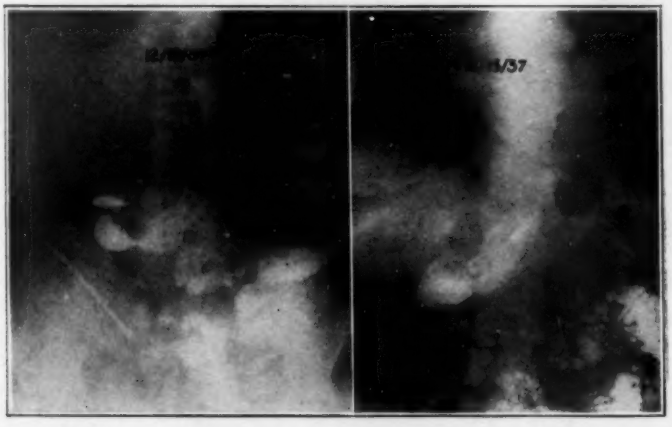

Fig. 11 (case 3).—Postoperative gastric roentgenograms showing an essentially normal picture.

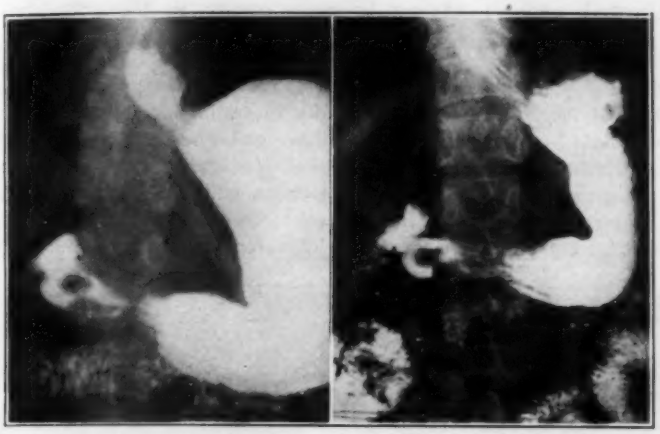

Fig. 12 (case 4).—Preoperative roentgenogram showing a persistent antral defect suggestive of a possibly benign neoplasm.

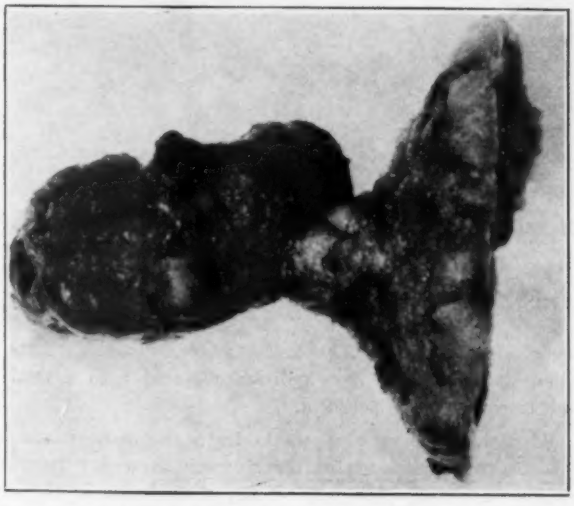

Fig. 13 (case 4).—Photograph of a gross specimen of a pedunculated tumor the size of a golf ball excised from the greater curvature of the stomach just above the pylorus.

This patient's first symptom was hemorrhage severe enough to force hospitalization for shock. Gastric roentgen studies done only ten days apart showed widely varying findings owing to the mobility of the tumor. This is not uncommon.

CASE 4 (Polypoid adenoma).—M. H., a 65 year old white woman, was admitted to the hospital Aug. 3, 1940, with difficulty in swallowing of approximately one year's duration. She had been known to have goiter for about seven years. The complaints which brought her into the hospital were marked weakness, dizziness and cardiac palpitation. She was an elderly woman who was extremely anemic. A large colloid goiter was present in the neck; other physical findings were essentially normal. On admission the hemoglobin content was 30 per cent; the red

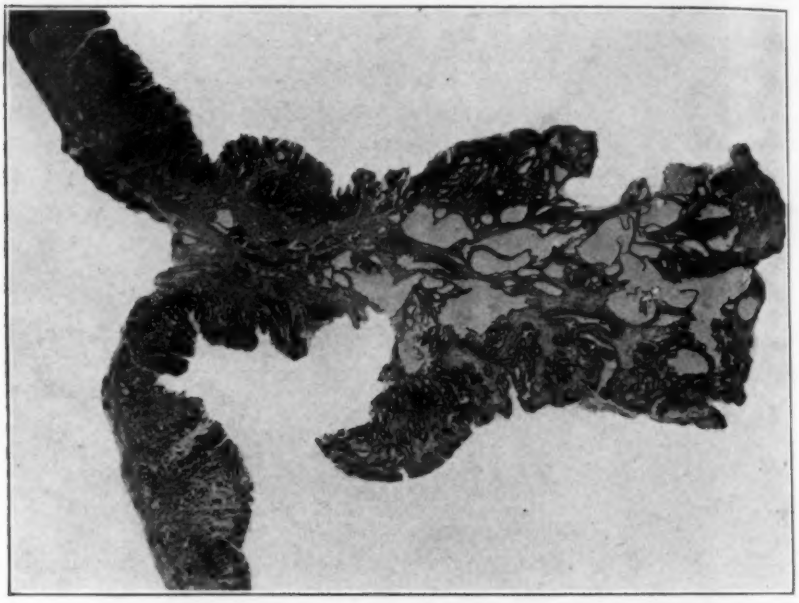

Fig. 14 (case 4).—Low power photomicrograph of a specimen reported as polypoid adenoma.

blood cell count was 2,500,000. The stools gave a positive reaction for blood, and gastric analysis showed no free hydrochloric acid with a total of 50. The basal metabolic rate was + 28 per cent.

Course.—The patient was worked up to learn the cause of the anemia. On September 9 roentgen examination of the stomach showed a translucent area in the pyloric region of the stomach without any disturbance in the contour of the rest of the stomach. This was interpreted as a benign polyp. An episternal and substernal thyroid was also found on roentgen examination. The patient was given three blood transfusions; the hemoglobin content rose to 74 per cent and the red blood cell count to 4,200,000.

Operation was done on September 12. A polypoid adenoma 2 by 1 cm. attached to the greater curvature just above the pylorus was locally excised. The patient had an uneventful postoperative recovery and was discharged on the

twentieth postoperative day. She returned a month later; at that time thyroidectomy was done. She was discharged on the fourteenth postoperative day. At the time of writing she has been followed for one year and is in excellent condition. Incidentally, gastric acidity has returned to normal levels.

Gross Pathologic Examination.—The specimen consisted of a pedunculated piece of tissue 2 by 1 cm. It was oval and hung from a stem attached to a base which was 2 by 2 by 1 cm. On section the base was observed to be white and the tumor part reddish brown.

Microscopic Examination.—The base consisted of mucosa and submucosa. The mucosa was typical gastric mucosa. A fibrous tissue stem extended out to the tumor. This stem contained blood vessels and occasional dilated acini lined with mucous cells. The mass itself consisted of dilated acini lined with mucous cells.

Fig. 15 (case 4).—High power photomicrograph of the specimen shown in figure 14.

There was considerable inflammatory cell invasion of the interacinous tissues, and edema was present.

Pathologic Diagnosis.—The pathologic diagnosis was benign gastric polyp (figs. 12 to 15).

Case 5 (Adenomatous polyp, ulcerated).—T. G., a 51 year old white man, was admitted to the hospital Jan. 2, 1930, with a four months' complaint of increasing weakness with some nausea. There was no other significant history. The patient had anemia; the red blood cell count was 2,500,000; and the hemoglobin content was 35 per cent. In the course of work-up to learn the cause of the anemia, gastric roentgen examination was reported January 7 as follows: The barium sulfate on entering the duodenum surrounded the outer circumference with a central translucent area suggesting the presence of a polyp of the stomach or the duodenum.

Operation was done on February 28. A pedunculated tumor the size of an orange attached to the greater curvature 2½ inches (6.35 cm.) above the pylorus

Fig. 16 (case 5).—Preoperative roentgenogram showing barium sulfate surrounding a translucent area in the duodenum indicative of prolapse of the tumor through the pylorus.

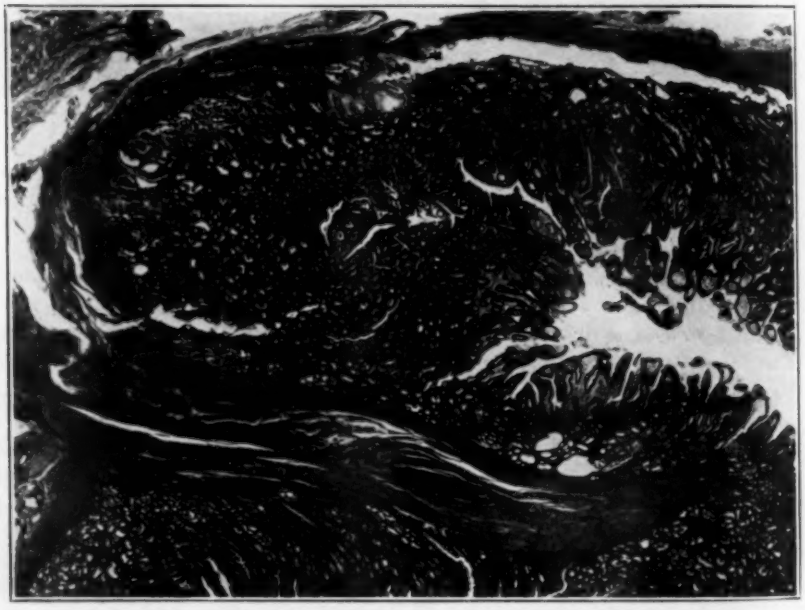

Fig. 17 (case 5).—Photomicrograph of a specimen reported as adenomatous polyp.

was excised. This had prolapsed through the pylorus and was widely ulcerated. The patient was in poor condition at the time of operation and died on the third postoperative day of bronchopneumonia.

Pathologic Diagnosis.—The pathologic diagnosis was adenomatous polyp.

The finding of this adenomatous polyp was incidental to the diagnosis of the cause of severe anemia. The ulceration and prolapse through the pylorus without doubt accounted for the severity of symptoms (figs. 16 and 17).

CASE 6 (Adenomatous polyp with gastric ulcer).—E. K., a 53 year old white man, was admitted to the hospital Nov. 10, 1937, with a history of epigastric pain, nausea and vomiting of three months' duration and loss of 20 lb. (9.1 Kg.) in one year. The patient was emaciated. The red blood cell count was 3,900,000.

Fig. 18 (case 6).—Preoperative roentgenogram showing a pyloric defect with gastric retention interpreted as possible carcinoma.

The hemoglobin content was 80 per cent. The stools gave a 3 plus reaction for blood. Roentgen examination on November 12 was reported to show gastric retention with defect at the pylorus. Preoperatively a diagnosis of carcinoma was made.

On November 30 subtotal gastric resection with posterior Polya anastomosis was done because the tumor of the stomach was adherent to the liver and thought to be malignant. The patient made an uneventful recovery after operation.

Gross Pathologic Examination.—A gastric ulcer on the lesser curvature with four polyps the size of walnuts on the greater curvature at the pylorus was found by macroscopic examination.

Microscopic Examination.—The microscopic examination was reported to show an adenomatous polyp of the stomach with a gastric ulcer of the lesser curvature.

This patient had a benign adenomatous polyp on the greater curvature and a gastric ulcer on the lesser curvature (figs. 18 and 19).

Fig. 19 (case 6).—Photomicrograph of an adenomatous polyp of the greater curvature of the stomach removed by gastric resection. It was associated with a gastric ulcer of the lesser curvature.

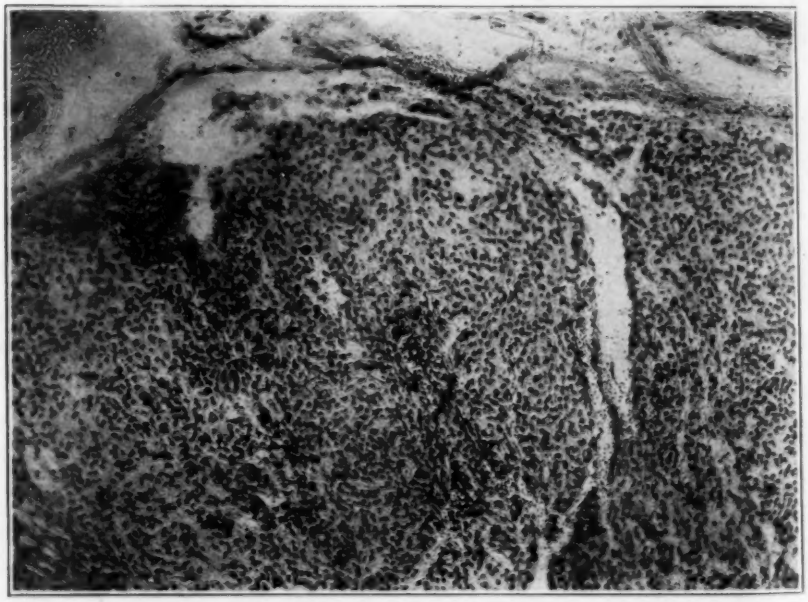

Fig. 20 (case 7).—Photomicrograph of a rare type of benign gastric tumor. The pathologists reported this to be hemangioendothelioma.

CASE 7 (Hemangioendothelioma).—P. B., a 56 year old white man, was admitted to the hospital Sept. 4, 1929, with a twenty year history of indigestion and recent onset of weakness, nausea, vomiting and loss of weight. He was chronically ill, emaciated and had a red blood cell count of 2,200,000 and a hemoglobin content of 22 per cent. Roentgen examination on September 10 was reported to show a well defined pyloric lesion with loss of rugose markings. A benign tumor was suspected because of the perfect regularity of the greater and lesser curvatures. A diagnosis of possible benign pyloric tumor was made.

Operation was done on September 17. By gastrotomy a multilobular well encapsulated tumor at the pylorus was removed. It was firm with some semi-cystic areas and was readily shelled out from beneath the mucosa, which was

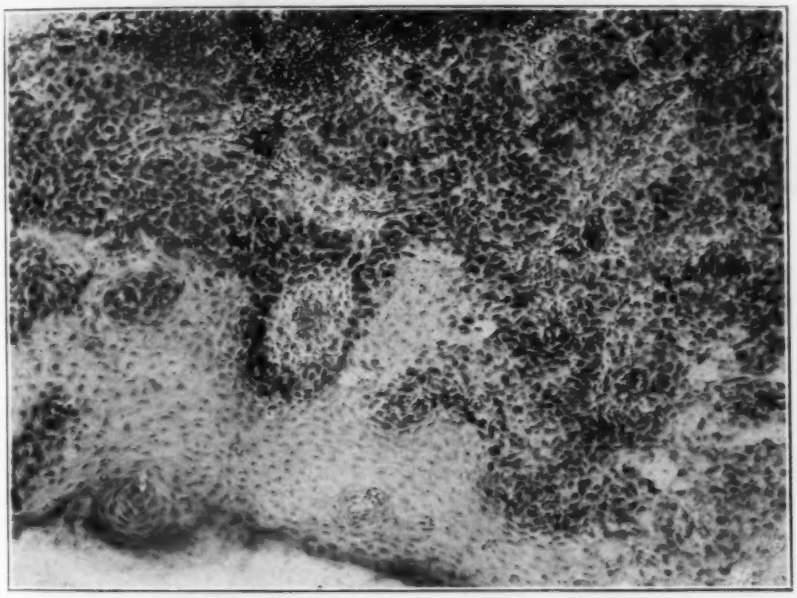

Fig. 21 (case 8).—Photomicrograph of a rather rare type of benign gastric tumor. This was reported to be cellular fibroma.

not ulcerated. The patient made an uneventful recovery and was followed for four years; when last seen, he was perfectly well.

Pathologic Report.—Since this was a rather rare type of tumor, we shall give the complete pathologic report: The mass showed thin-walled small blood vessels embedded in richly cellular tissue with the cells of indefinite histologic nature. The preponderant cell was small and sharply outlined and had a sharply limited membrane. The cytoplasm stained lightly. The nucleus was small, oval and poorly chromatic. There were small thin-walled vessels; single and in groups, lined with endothelium.

Pathologic Diagnosis.—The pathologic diagnosis was hemangioendothelioma (fig. 20).

CASE 8 (Cellular fibroma[?]).—C. B., a 60 year old white woman, was admitted to the hospital May 7, 1925, with six weeks' history of epigastric pain, nausea

and vomiting with slight initial jaundice and a loss of 40 lb. (18.1 Kg.). She was chronically ill and slightly icteric and had a tender abdomen and an enlarged liver. Stools gave a positive reaction for blood. The red blood cell count was 1,600,000 and the hemoglobin content 28 per cent. Seven days after admission the patient vomited 14 oz. (4.14 cc.) of material resembling coffee grounds which gave a positive reaction for blood. Six days later increasing icterus was noted, and the stools became clay colored. Roentgen examination showed a gastric neoplasm at the pylorus. Preoperatively a diagnosis of obstruction of the common duct was made, probably from an extension of pyloric carcinoma.

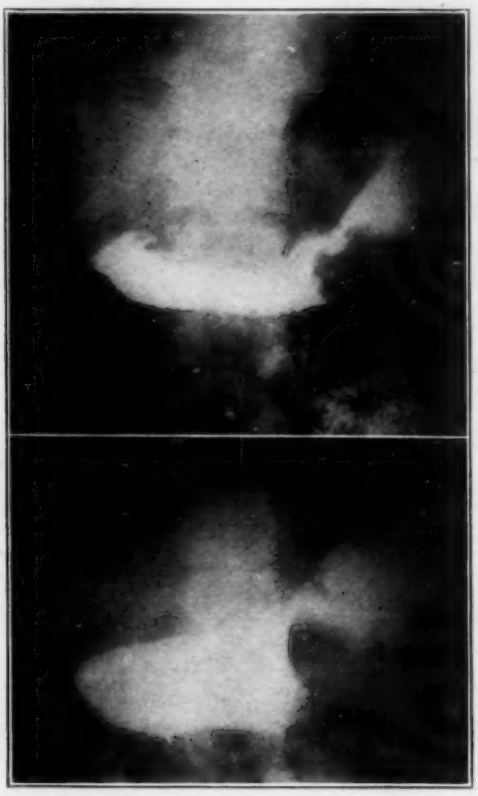

Fig. 22 (case 9).—Preoperative roentgenogram showing a well outlined tumor in the lumen of the stomach with a crater at the apex.

Operation was done on May 25. A common duct stone was removed from the ampulla by duodenotomy with drainage of the common duct. A large sessile ulcerated mass at the lesser curvature on the posterior wall near the pylorus was easily removed by gastrotomy. The patient made an uneventful recovery and at the time of writing has been followed for over ten years, being perfectly well at the age of 75 (fig. 21).

Pathologic Report.—The tumor was somewhat lobulated and exceedingly soft and friable. It appeared to be vascular. The tumor was entirely submucous and apparently did not involve the muscularis.

Microscopic Examination.—Sections taken from different areas showed dissimilar histologic pictures. In parts the tumor showed a cellular mass of long spindle connective tissue cells of adult character. Other sections suggested an epithelial origin, but they did not resemble cells derived from glandular epithelium. The general impression was that the tumor was a cellular fibroma.

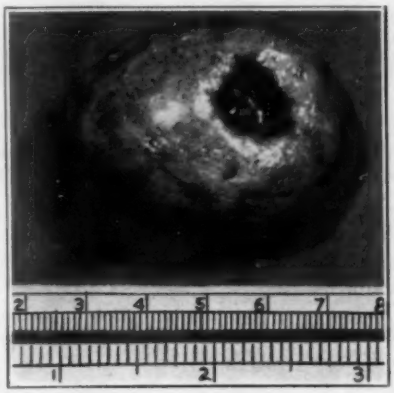

Fig. 23 (case 9).—Gross specimen showing an ulcer at the apex.

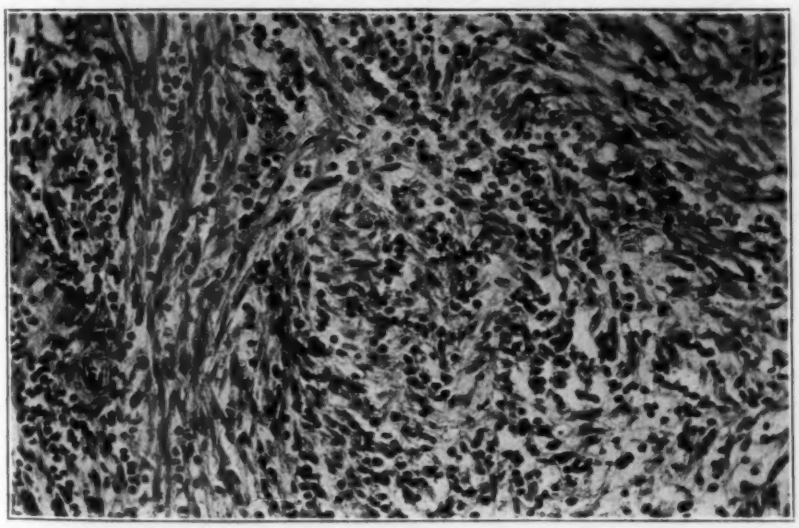

Fig. 24 (case 9).—Photomicrograph of a specimen reported by the pathologist to be leiomyoma of the stomach with chronic ulcer.

Case 9 (Leiomyoma).—G. O'B., a 57 year old white man, was admitted to the New York Hospital on Dec. 3, 1941. Four months previous to admission, while at work, he suddenly fainted and was told that he had vomited a large amount of blood. He was admitted to another hospital as an emergency patient, and a diagnosis of bleeding duodenal ulcer was made. After receiving several blood transfusions and dietary treatment, he was discharged from the hospital to

have roentgen studies of the stomach made in about two weeks. At this time the gastrointestinal roentgen series did not show a duodenal ulcer; neither was a positive diagnosis of benign tumor made. About two weeks before admission to the New York Hospital another gastrointestinal series was reported as showing a regular filling defect in the distal third of the stomach without obstruction. A diagnosis of benign tumor of the stomach with ulceration of the tumor, probably leiomyoma, was made.

At operation on December 6 a tumor the size of a golf ball attached by a broad pedicle to the posterior wall of the stomach along the greater curvature in the distal third was removed through gastrotomy. The patient made an uneventful recovery and was discharged from the hospital on December 20.

Gross Pathologic Examination.—The tumor was the size of a golf ball and had a punched-out ulcer 1.5 cm. in diameter at its apex. The center of the tumor was moderately soft, secondary to some degeneration.

Microscopic Examination.—Microscopic examination showed leiomyoma of the stomach with a chronic ulcer with some hypertrophy and degeneration of interlacing bundles of smooth muscle.

This is another instance of the onset of symptoms with severe hemorrhage in a previously well person.

SUMMARY AND CONCLUSIONS

In 108 cases of benign gastric tumor 76 of the lesions were found at autopsy and 32 at operation. For various reasons the vast majority of these were not correctly diagnosed previous to death or operation. Many remained practically asymptomatic without apparent detriment to the person. Others, however, produced alarming symptoms, the complexity of which often led to error. Practically all of the mistakes can be traced to confusion with either gastric carcinoma or bleeding peptic ulcer.

With the benign tumor pyloric obstruction and hemorrhage are the common complaints requiring treatment and combine with the occasional close resemblance to carcinoma or peptic ulcer on roentgen examination to account for most of the errors. Although these similarities have been recognized, some points of value in differential diagnosis have been singled out and described as the experience of this study.

The hazards of severe hemorrhage and malignant degeneration constitute valid indications for surgical treatment of all benign gastric tumors. Local excision usually suffices except for the sessile adenomatous polyps at the pylorus. Gastric resection is probably indicated in this subgroup of tumors in view of the high incidence of malignant degeneration.

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CYSTS OF THE PANCREAS

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In spite of the infrequent occurrence of cystic disease of the pancreas, the condition not only is of interest from the pathologic point of view but also is of practical importance. Cystic disease of the pancreas has long been recognized as a clinical entity. Its symptoms have been adequately described; its causation has been surmised, and certain of its pathologic aspects have been studied.

The basis of this report is a study of 17 cases of cysts of the pancreas. This includes all the cases collected from the records of Jewish Hospital. In 14 cases operation was performed. In some cases it was difficult for the operating surgeon to identify the cyst in relation to the surrounding structures and to determine whether it was a true pancreatic cyst or a so-called pseudocyst. In only 1 case was the tumor malignant.

AGE AND SEX INCIDENCE

Pancreatic cyst may occur at any age but is most often seen in persons about middle life. Telling and Dobson [1] described a case in which the patient was an 11 month old child. The ages of the patients in this series ranged from 21 to 76 years, averaging 45.4. The age period of greatest frequency was from 21 to 49 years. There were 14 female and 3 male patients, showing a preponderance of the disease among female patients.

PATHOGENESIS

Owing to lack of knowledge concerning the pathogenesis of the various types of pancreatic tumor, classifications are necessarily at variance. Robson and Moynihan [2] grouped these neoplasms as retention cyst, proliferative cyst (including cystic adenoma and cystic epithelioma), hydatid cyst, congenital cystic disease, hemorrhagic cyst and pseudo-

From the Departments of Surgery and Pathology, Jewish Hospital.

1. Telling, W. H., and Dobson, J. F.: Pancreatic Cyst in an Infant, Brit. J. Child. Dis. **6**:202, 1909.

2. Robson, A. W. M., and Moynihan, B. G. A.: Diseases of the Pancreas and Their Surgical Treatment, Philadelphia, W. B. Saunders Company, 1903, p. 188.

cyst. Judd's [3] inclusion of dermoid cyst seemed to complete the list. Analysis of the series on which this study is based, however, has disclosed another form of pancreatic cyst which to our knowledge has not been heretofore described in the literature. As will be seen later, this tumor originates from Brunner's glands included in the pancreas because of some fault in embryonic development.

An outline of the different forms of pancreatic cyst described in this paper is given in table 1.

It is the consensus that pseudocyst is more frequent of occurrence than the other forms of cystic tumor of the pancreas; this also holds true in this series. The cyst may occur in any portion of the organ although it is most prevalent in the tail.

The origin of pancreatic cyst has been a matter of conjecture since it was first described. The pathologic description of the growth encountered in the reported cases makes one suspect that in the majority of instances the lesion is the result of some form of trauma to the

TABLE 1.—*Types of Pancreatic Cyst Encountered in This Study*

Type of Cyst	Cases
Pseudocyst	11
Cystadenoma	2
Retention cyst	2
Inclusion cyst (Brunner's gland)	1
Cyst with carcinomatous changes	1

pancreas. This is particularly significant with regard to pseudocyst. Körte [4] proposed the term "pseudocyst" for a fluid tumor found in more or less close proximity to the pancreas but not originating in the substance of the gland, the most frequent examples being those of effusion into the lesser sac of peritoneum as a result of injury to the pancreas. Lloyd [5] was among the first to point out that the majority of pseudocysts following abdominal injury were not true retention cysts of the pancreas. He reported 2 cases, both occurring after abdominal injury —one three weeks and another three months after trauma. He expressed the opinion that both were associated with injury to the pancreas, probably by pressure against the first lumbar vertebra. Willis and Budd [6] restricted the term "pseudocyst" to a cyst resulting from trauma.

3. Judd, E. S.: Cysts of the Pancreas, Minnesota Med. **4**:75, 1921.

4. Körte, W.: Zur Behandlung der Pankreaszysten und Pseudozysten, Deutsche med. Wchnschr. **37**:536, 1911.

5. Lloyd, J.: Injury to the Pancreas: A Cause of Effusion into the Lesser Peritoneal Cavity, Brit. M. J. **2**:1051, 1892.

6. Willis, A. M., and Budd, S. W.: Pancreatic Cysts, with Report of a Case, Surg., Gynec. & Obst. **20**:688, 1915.

Of 117 cases collected from the literature by Körte in 1911 there was a definite history of abdominal injury in 33. Among 41 cases collected by Judd in the records of the Mayo Clinic, trauma seemed to be a causative factor in 1 case only, the cyst occurring two months after the injury.

Experimental evidence also lends support to the view that trauma is an important causative agent in the production of pseudocyst of the pancreas. Lazarus[7] was able to produce such a cyst by crushing the pancreas of a dog. A hematoma first formed, which later became an encapsulated cyst and contained 100 cc. of milky fluid. These clinical facts together with the experimental evidence of Lazarus point to trauma as a factor in the production of pseudocyst of the pancreas.

While this conception of the causation of pseudocyst of the pancreas does not account for all cystic processes of this sort under all conditions, it offers a reasonable explanation of the majority of them and is in accord with the personal experience of many victims of the disease. Sufficient evidence has accumulated, however, which points to other agents besides trauma as causative factors. Thus it is well known that after certain inflammatory conditions of the pancreas or the gallbladder pseudocyst may develop in the pancreas. It is also of importance to note that in many instances no cause whatsoever could be discovered to account for the formation of the cyst. In none of our patients was a history of trauma elicited, nor was any coexisting condition found which could have been responsible for the hemorrhage in the pancreas. In the first 11 of the following cases the growth was a pseudocyst.

REPORT OF CASES

Case 1.—C. G., a woman aged 56, was admitted to the hospital with generalized abdominal pains of several years' duration. The cramps were said to be relieved by catharsis and enemas. During the last six months before admission the cramps became intensified, and the abdomen increased in size. She had lost considerable weight and grown weaker, and swelling of the lower extremities developed. Physical examination at the time of admission revealed an emaciated woman. The abdomen was large and tense and was the seat of a tender mass which extended from the pelvis to about 3 fingerbreadths above the umbilicus. There was evidence also of free fluid in the peritoneal cavity. A diagnosis of retroperitoneal tumor was made, and the abdomen was opened through a median lower incision. The abdominal cavity contained a large amount of free straw-colored fluid and a large retroperitoneal cyst the anterior surface of which was adherent to the parietal peritoneum. The cyst appeared to arise in the region

7. Lazarus, P.: Beitrag zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Zysten und Steine, Ztschr. f. klin. Med. **51**:95 and 203, 1904.

of the body of the pancreas; it was aspirated, and a thick gelatinous brown fluid was obtained. The cyst was drained, and the patient made an uneventful recovery. Chemical examination of the aspirated fluid showed mucus, diastase and trypsin.

CASE 2.—E. F., a 35 year old housewife, was admitted to the hospital with persistent vomiting of eighteen hours' duration. During a routine examination two months before, her physician had discovered a lump in the left upper quadrant of the abdomen. She lost considerable weight and was subject to attacks of headaches and dizziness. Cholecystectomy and appendectomy were performed three years previously. She was well developed and well nourished but apparently extremely ill; she retched constantly. In the left hypochondrium there was a round, firm, ballotable and nontender mass about the size of a grapefruit. Roentgen examination showed displacement of the stomach upward and to the right by a large extrinsic soft tumor mass which also encroached on the greater curvature. Examinations of the blood and the urine revealed no abnormalities. A diagnosis of omental or pancreatic cyst was made. At operation a large blue cystic tumor was observed occupying the lesser sac. It displaced the ascending layer of the transverse mesocolon upward. The tumor was approached through the gastrocolic omentum; the wall was incised, and several quarts of blood-stained fluid together with coagulated and necrotic debris was evacuated. The cystic wall was marsupialized to the anterior abdominal wall, and three cigaret drains were left in situ. A small portion of the cyst was removed for examination. The wound continued to drain for two weeks; during this time a clear fluid was discharged in decreasing amounts. The patient made complete recovery in six weeks.

Biopsy showed part of the surface wall to be covered with cylindric epithelium. The rest of the wall consisted of dense layers of granulation tissue infiltrated in places with round cells, large mononuclear cells and some polymorphonuclear leukocytes. Another portion of the surface was thrown into coarse folds, and in the deeper layers were spaces lined by low cuboid cells as well as tubular and duct structures lined by cylindric cells.

CASE 3.—S. H., a 47 year old woman, was admitted to the hospital with the complaint of severe abdominal pain, distention and vomiting of three weeks' duration. She complained also of continuous cutting pains in the lumbar region; she had lost considerable weight.

On examination the patient was observed to be well developed and well nourished and apparently not acutely ill. There was tenderness over the hypogastrium and the right hypochondrium but more particularly in the region of the gallbladder. No masses could be palpated in the abdomen. The laboratory findings included: blood sugar, urea, creatinine and cholesterol; these were normal. A Wassermann test of the blood had a negative result; the blood count was normal; the urine was normal. Roentgen examination of the stomach revealed retention of barium sulfate after a six hour period. The normal acute angle at the junction of the first and second portions of the duodenum was changed to almost a semicircular form, indicating separation of the first and second duodenal segments by enlargement of the head of the pancreas. A diagnosis of pancreatic tumor was made, and at operation a large mass the size of a fetal head could be felt extending from the ensiform process to the umbilicus. The stomach was diplaced to the left and downward, and the gastroepiploic omentum was pushed forward by a mass immediately under it. Aspiration of this mass yielded more

than a liter of light gray fluid mixed with blood and globules of oil. The gallbladder was markedly distended. Drainage of the cyst was effected through marsupialization to the anterior abdominal wall; the gallbladder also was drained. Chemical analysis of the aspirated fluid revealed an alkaline reaction, a specific gravity of 1.014, the presence of cholesterol, trypsin and albumin but no bile. Microscopic examination of the fluid showed debris, cholesterol crystals, fatty acids, fat globules and desquamated epithelium. Culture of the fluid was sterile.

The postoperative course was complicated by excoriation of the skin. This was treated with Beck's paste and zinc oxide. The patient was discharged forty-five days later well improved.

Case 4.—F. F., a 21 year old woman, was admitted to the hospital because of rapid enlargement of the abdomen during the previous six months. This was associated with increasing constipation, dyspnea and frequency of urination. The appendix had been removed six years previously. On examination the patient was observed to be well developed and well nourished. The abdomen showed a huge tumor mass extending from the symphysis pubis to 6 fingerbreadths above the umbilicus and to both flanks. The mass was firm and dull to percussion. A diagnosis of ovarian cyst was made.

At operation a cyst about the size of a large melon could be felt in the retroperitoneal tissues in the upper portion of the abdomen, probably arising from the pancreas. Projecting upward from this mass, another smaller cyst the size of an orange could be felt. Aspiration of the mass yielded a considerable amount of dark hemorrhagic liquid material. The cyst was incised; its contents were evacuated, and the wall was marsupialized. Three drains were left in situ. The patient made an uneventful recovery.

Examination of the aspirated fluid revealed the following: Culture was sterile. There was amylase but no trypsin or bile. Cytologic examination revealed degenerated polymorphonuclear leukocytes and lymphocytes.

Case 5.—L. D., a 23 year old woman, was admitted to the hospital with the complaint of epigastric distress and constipation of six days' duration. Three days after the onset of her illness the pain radiated to the right lower quadrant of the abdomen and became sticky in character. When examined, the abdomen was soft and nontender, and no masses were palpable. A diagnosis of chronic appendicitis was made. At operation a retroperitoneal cyst the size of a plum was found in the region of the pancreas and was excised. The appendix also was removed.

Grossly, the excised specimen consisted of a cystic mass 3.5 cm. in diameter. The external surface was pearly white, smooth and glistening; the internal surface was smooth. The contents of the cyst consisted of yellow-gray mucoid material mixed with some necrotic debris. Chemical examination of this fluid revealed the presence of amylase. Microscopic examination of the cyst showed a portion of the wall surface lined by low cuboid cells; other areas were completely denuded of cell covering. The rest of the cyst wall consisted of dense layers of fibrous connective tissue in which were scattered a moderate number of lymphocytes and occasional small hemorrhages.

Case 6.—J. G., a 31 year old woman, was admitted to the hospital with the complaint of pain in the left upper quadrant of the abdomen. Eight months previously she had been seized with an attack of pain in the left upper quadrant,

nausea, vomiting and diarrhea. She was confined to bed for ten days and felt much improved. Two months later the pain recurred with flatulence and distention. Since then she had been subject to repeated attacks of abdominal pain which came at intervals of two to four weeks. Two weeks before admission she had a sharp attack of pain in the left upper quadrant; this radiated to the left shoulder and the left side of the neck and was aggravated by deep breathing.

On examination the patient did not appear acutely ill. The abdomen presented an irregular nontender firm mass in the left upper quadrant, which moved freely with respiration. Roentgen examination of the chest and the gastrointestinal tract revealed no abnormalities. A diagnosis of pancreatic cyst was made, and the abdomen was opened through a left subcostal incision. A large cystic tumor about the size of a grapefruit was found in the tail of the pancreas. It extended upward under the diaphragm and downward posterior to the stomach and the spleen. Eight hundred cubic centimeters of old fluid blood was aspirated and found to contain amylase. Microscopic examination of a portion of the cyst wall showed dense layers of fibrous and hyalinized connective tissue enclosing numerous thin-walled blood vessels, lymphocytes and small areas of hemorrhage. The surface was denuded of epithelium.

Case 7.—F. K., a 41 year old woman, was admitted to the hospital with sticking pains and a mass felt in the left upper quadrant of the abdomen. These complaints had been present for six months. The tumor began to grow at an extraordinarily rapid rate, and at the end of six months it filled the upper part of the abdomen.

On examination the patient was observed to be well developed and well nourished and restless. The abdomen was the seat of a huge tumor mass which occupied its entire left side. The mass felt partly semisolid and partly cystic.

Roentgen examination revealed a tremendous soft tissue mass occupying almost the entire left side of the abdomen, extending well below the crest of the ilium and reaching across the right side of the midline. A clysma of barium sulfate showed deviation of the transverse colon to the splenic flexure by a large mass in the left upper quadrant of the abdomen. A film taken in the lateral projection showed that this mass pushed the bowel anteriorly. Roentgen examination of the upper part of the gastrointestinal tract showed the stomach displaced anteriorly. These findings indicated that the mass probably originated in the region of the pancreas.

The laboratory findings were as follows: The icteric index was 5.8. The blood sugar content was 87 mg. per hundred cubic centimeters. The blood urea content was 10.2 mg. per hundred cubic centimeters. Cutaneous tests for ecchinococcic cyst gave negative results.

A diagnosis of retroperitoneal sarcoma was made, although the possibility of a pancreatic cyst was entertained. At operation a tumor was felt retroperitoneally; this suggested cyst of the pancreas. The tumor extended far down into the pelvis but had no pelvic connections. It soon became evident that this was a retroperitoneal cyst which had developed downward and forward. Aspiration of this mass yielded a dark brown hemorrhagic fluid; approximately 5 liters of this was aspirated from this cystlike mass. Drainage was instituted at the site of aspiration, and the cyst wall was marsupialized after a small piece was removed for pathologic examination. The patient made an uneventful recovery.

Chemical examination of the aspirated fluid showed that the pancreatic enzymes were present; there was no bile. The fluid was sterile on culture. Biopsy showed the cyst wall to be composed of loose fibrous connective tissue. The surface was denuded of epithelium.

CASE 8.—G. G., a 49 year old woman, was admitted to the hospital with the complaint of intermittent attacks of pain in the left upper quadrant of the abdomen of five months' duration. The pain was said to arise in the left costovertebral area and radiate along the costal margin to the left upper quadrant. It recurred at intervals of two to three weeks, lasted a week and then subsided. She complained also of constipation and of the loss of 10 pounds (4.5 Kg.) since the onset of the illness.

On examination the patient appeared well developed and well nourished and not acutely ill. A large ballotable mass was present in the left upper quadrant of the abdomen. It extended from about 2 fingerbreadths beyond the midline to the right and along the left costal margin; it moved freely with respiration. Examinations of the blood and the urine revealed no abnormalities. A diagnosis of cyst of the pancreas was made.

Fig. 1.—Photograph showing gross appearance of pseudocyst of the pancreas. The surface is partly smooth and partly roughened by fibrous tags.

At operation a left subcostal incision was made, and a large cyst about 20 cm. in diameter was noted in the tail of the pancreas. It contained about 800 cc. of turbid hemorrhagic fluid. The entire cyst was excised. The splenic artery had to be ligated to facilitate removal of the cyst, and consequently the spleen also was removed. Chemical examination of the aspirated fluid revealed the presence of lipase and amylase; there was no bile.

Grossly, the tumor consisted of a thick-walled, opaque and oval-shaped mass 12 cm. in diameter. The external surface was pink-gray, partly smooth and glistening and partly roughened by fibrous tags. The wall measured up to 0.2 cm. in thickness. The inner lining of the cyst was smooth, glistening and trabeculated (fig. 1).

Microscopically, the cyst wall consisted of dense layers of fibrous and hyalinized connective tissue. The inner surface was partly covered by a single layer of low cuboid epithelium (fig. 2).

The association of acute and chronic pancreatitis with the formation of these cysts is well established, and, in turn, the relation between infection in the gallbladder and the bile ducts as a causative factor, direct as to pancreatitis and indirect as regards cyst formation, must be taken into account. Analysis of our group of cases shows a definite relation between the development of acute pancreatitis and cholecystitis and

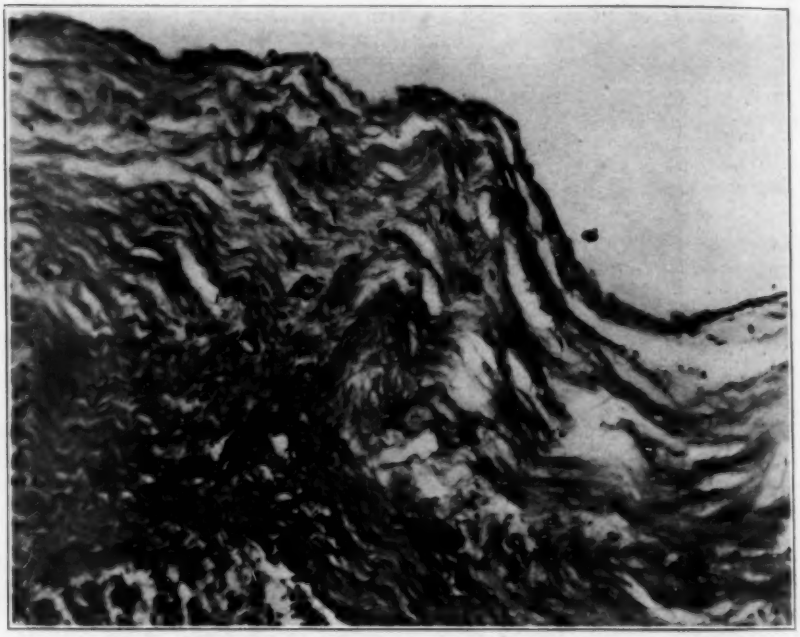

Fig. 2.—Photomicrograph showing the wall of the pseudocyst shown in figure 1. The inner surface is lined by a single layer of low cuboid epithelium. The rest of the wall is made up of dense layers of fibrous and hyalinized connective tissue.

the formation of some of these cysts. In 1 case pseudocyst of the pancreas was preceded by an attack of acute pancreatitis, and in 2 others it was preceded by attacks of acute cholecystitis.

CASE 9.—S. R., a 23 year old woman, was admitted to the hospital with the complaint of a sense of fulness and discomfort in the epigastrium of three months' duration. The pain radiated to the back and lasted several hours. For the last three weeks before admission the pain became more severe in character. On examination there was deep tenderness in the right hypochondrium and marked

spasm of the rectus muscles. A diagnosis of acute pancreatitis was made, and at operation a large quantity of serosanguineous fluid was found in the peritoneal cavity; there was evidence also of fat necrosis. After drainage was instituted, the abdomen was closed. The patient made a complete recovery and was discharged from the hospital three weeks later.

She returned after three months because of enlargement of the abdomen. Abdominal examination revealed a small tumor in the right upper quadrant; this was freely movable and was cystic in consistency. At operation a small cyst was observed in the region of the tail of the pancreas. The cyst was aspirated, and 45 cc. of sanguineous fluid was removed. The patient made an uneventful recovery. Chemical analysis was made of the aspirated fluid. The specific gravity was 1.025. The fluid gave an alkaline reaction. It contained no bile. Amylase was present, but there was no trypsin. The fluid gave a positive reaction to the guaiac test for blood.

Case 10.—H. W., a 48 year old woman, was admitted to the medical service with the complaint of headaches, nausea, vomiting and pain in the back radiating to the epigastrium of ten years' duration. During the past eighteen months sharp stabbing pain had developed in the right costovertebral area and radiated to the front of the abdomen. This was followed by nausea and vomiting. The attacks usually occurred in the early hours of the morning and required the administration of morphine sulfate for relief. The attacks were most prone to occur after the patient had partaken of a fatty meal.

On examination the patient was observed to be well developed, rather obese and not acutely ill. The abdomen presented a tender area just to the right and above the umbilicus. A diagnosis of nephrolithiasis was made. While the patient was in the hospital, an acute attack of pain in the back which radiated to the right upper quadrant developed. Icterus soon developed, and bile appeared in the urine. The patient was transferred to the surgical service, and at operation an acutely inflamed gallbladder was found and removed. Her postoperative course was complicated by increasing jaundice, rise in temperature and severe pain in the left upper quadrant of the abdomen and in the back. On the sixteenth postoperative day the temperature rose to 103 F.; the abdomen became distended; there was fulness in the left flank, and large quantities of bile escaped through the wound. Roentgen examination revealed a large homogeneous opacity with well defined margins suggestive of a cystic mass in the left upper quadrant of the abdomen. Intravenous pyelographic examination revealed nothing unusual. The patient was operated on again six weeks after removal of the gallbladder, and a large retroperitoneal cystic mass about the size of a football was found in the region of the pancreas. The cyst was incised, and approximately 4 quarts (3.8 liters) of green fluid was evacuated. It was then marsupialized, and two drains were left in situ. The patient made an uneventful recovery.

Pathologic examination of the cyst wall showed it to consist of lobules of adipose tissue and dense bands of hyalinized connective tissue enclosing numerous newly formed capillaries, round cells, polymorphonuclear leukocytes and eosinophils. Chemical analysis of the aspirated fluid showed a small amount of bile, amylase and lipase. Culture of the fluid was sterile.

Case 11.—L. B., a 72 year old woman, was admitted to the hospital with a history of progressive jaundice of six weeks' duration and clay-colored stools,

itchiness and general abdominal pain of four weeks' duration. She had lost some weight. Eleven years previously posterior gastroenterostomy had been performed for duodenal ulcer.

On admission the patient was observed to be well developed, obese and icteric. A moderately tender mass was present in the right upper quadrant of the abdomen. The icteric index was 50; urea was 73; total cholesterol was 213 mg. per hundred cubic centimeters, and free cholesterol was 63 per cent. Phosphatase was 10.6, and sugar was 83.

A diagnosis of carcinoma of the pancreas was made, and at operation there was found an acutely inflamed thick-walled gallbladder with two stones lying free in its cavity and another stone impacted in the cystic duct. In addition, the head of the pancreas was the seat of a cyst about the size of an orange. The cyst was incised; its contents were aspirated, and the wall was marsupialized. The gallbladder was drained. After operation the jaundice subsided, and the patient was discharged on the fourteenth postoperative day well improved.

Cystadenoma of the pancreas is not a common finding; it occurred in 2 cases in our series. The tumor is usually small and well circumscribed and arises from the parenchyma of the pancreas. Cystadenoma is therefore a true pancreatic tumor and is distinguished from retention cyst by the abundant growth of epithelial papillae.

Case 12.—E. S., a 28 year old man, was admitted to the hospital because of blood in the stools and sharp pain in the lower part of the abdomen of two days' duration. He was known to have suffered from peptic ulcer for ten years, and he had been receiving a Sippy diet for the last four years before admission.

On examination the abdomen presented nothing unusual. The stools gave a strong positive reaction for blood. A diagnosis of bleeding duodenal ulcer was made. For this he was operated on through an upper right rectus incision. As the peritoneal cavity was opened, a small mass 4 inches (10.2 cm.) in diameter was found in the head of the pancreas. A small ulcer also was found on the anterior surface of the first portion of the duodenum. The cyst was excised, and the abdomen was closed after drainage was instituted at the site of excision.

Grossly, the specimen consisted of a multiloculated cyst 6 by 3 by 0.8 cm. The external surface was partly smooth and glistening and partly rough and irregular in outline. On section it was observed to contain a milky fluid. Microscopically, the cyst wall itself was thin, being made up of loose fibrous tissue and smooth muscle bundles, lined on its inner surface by a single layer of somewhat flattened epithelial cells. The connective tissue was infiltrated in places with round cells.

Case 13.—S. L., a 45 year old woman, was admitted to the hospital because of epigastric distress of five months' duration. On examination the patient was seen to be well developed and well nourished and not acutely ill. The abdomen presented a small mass in the upper quadrant just to the left of the midline. Roentgen examination of the gastrointestinal tract revealed no significant findings. A diagnosis of pancreatic cyst was made.

At operation performed by one of us (J. R.) there was found a small cyst arising from the midportion of the body of the pancreas. The cyst was excised,

and the abdomen was closed. Grossly, the specimen consisted of a multiloculated cyst 5 cm. in diameter. The wall was thin, and the contents consisted of a pale green watery fluid. Microscopically, the cyst wall was composed of loose bands of fibrous connective tissue which was thrown into numerous papillary folds lined by cuboid epithelium. In places the epithelium was heaped up and formed several layers of cells (fig. 3).

Chemical analysis of the cystic fluid revealed the presence of amylase.

Retention cyst of the pancreas is usually small and of little clinical or pathologic significance. It is said to arise as a result of obstruction

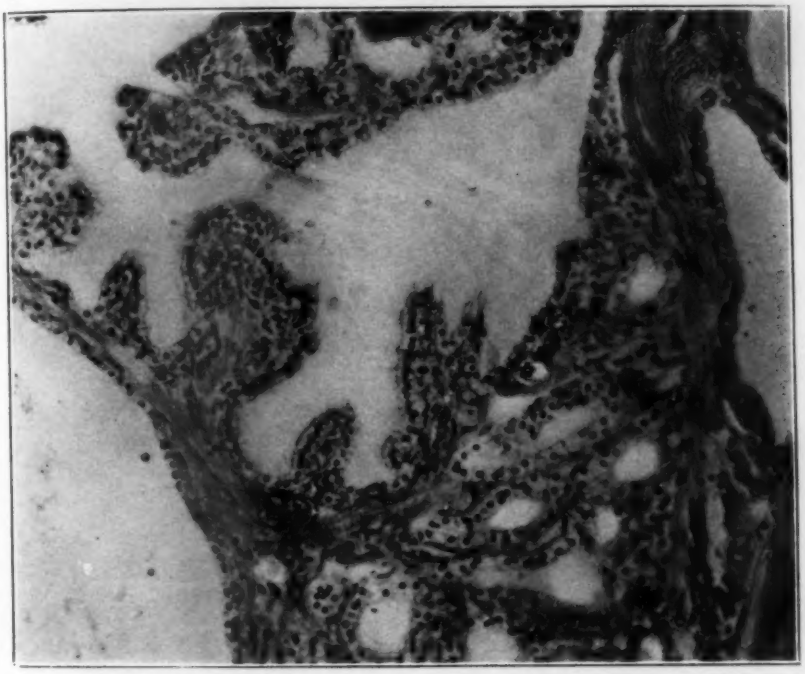

Fig. 3.—Photomicrograph showing cystadenoma of the pancreas. The section shows a multiloculated cyst lined by cuboid epithelium with many papillary projections also lined by cuboid cells.

to the pancreatic duct caused by calculi, tumor or chronic pancreatitis. In the necropsy records of the hospital we were able to find 2 cases of retention cyst of the pancreas in which operation was not done.

Case 14.—R. L., a 70 year old woman, was admitted to the hospital because of cardiac failure and general arteriosclerosis. She died shortly afterward, and at autopsy there was found in addition to cardiac hypertrophy a small cyst in the pancreas. The wall was thin and translucent, and the contents consisted of a cloudy pale yellow fluid.

Microscopically, the cyst wall was observed to be composed of loose fibrous tissue partly covered on its inner surface with flat epithelium (fig. 4).

CASE 15.—W. R., a 76 year old man, entered the hospital with the diagnosis of coronary thrombosis. He died several days later. At autopsy there were found in addition to coronary thrombosis and myofibrosis cordis multiple cysts of the pancreas. Microscopically the cyst walls were observed to be made up of a layer of fibrous connective tissue lined on one side by a single layer of low epithelium. The rest of the pancreas showed marked fibrosis.

The embryologic development of the pancreas and the morphologic relation of the pancreas to neighboring structures are of unquestioned significance in the production of certain forms of pancreatic cyst. From

Fig. 4.—Photomicrograph showing retention cyst of the pancreas. Much of the epithelium lining the cyst is denuded and thrown into the cavity of the cyst. The rest of the cyst wall consists of a thin layer of loose fibrous tissue.

the embryologic standpoint it is conceivable that remnants of duodenal tissue can become lodged within the pancreas. It is also possible for portions of these embryonic structures to migrate in the retroperitoneal tissues to invade the pancreas and act as nuclei of pancreatic tumors in postnatal life. Maldevelopment in the form of misplaced portions of Brunner's glands or irregularities in the normal differentiation of cells has not been seen. However, when such a condition does arise, obstruction of these glands may lead to cyst formation, in which acini or even an entire lobule may be dilated and contain a mass of cell detritus with

varying amounts of mucin. This hypothesis explains the similarity in cell structure of these cysts in the pancreas to Brunner's glands. More rarely there occur large cysts reaching several millimeters in diameter and producing nodules in the pancreas. The cysts are lined with low cuboid epithelium, and the lumens are largely free from stainable substances.

It seems reasonable in view of what has been said to assume that cysts of the pancreas may also arise from misplaced Brunner's glands in the pancreatic tissue. As an illustration of such a possibility we cite the following case:

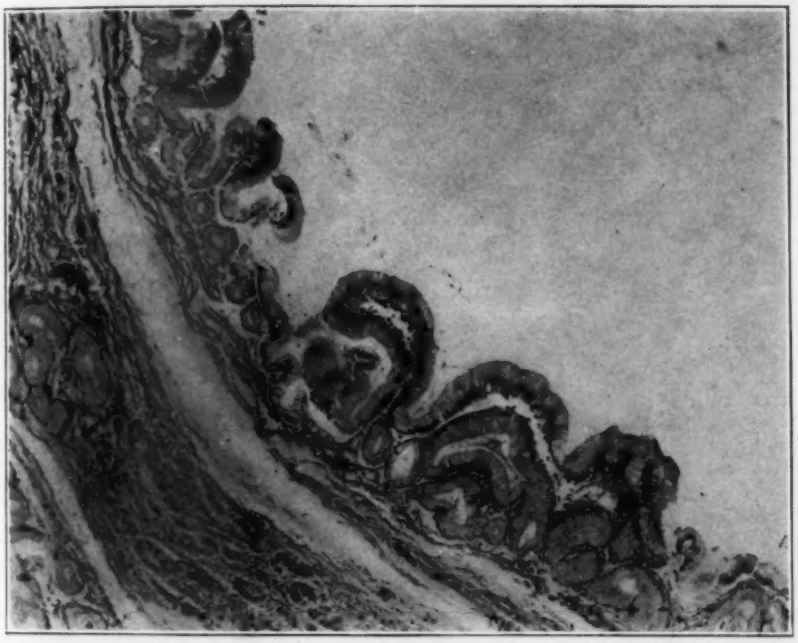

Fig. 5.—Photomicrograph showing Brunner's gland cyst of the pancreas. The innermost lining of the cyst is thrown into numerous folds lined by columnar mucous secreting epithelium. Immediately under this are islands of Brunner's glands and a thin layer of loose connective tissue. Scattered islands of Brunner's glands also are found within the pancreas.

Case 16.—D. F., a 42 year old man, died as a result of aortic stenosis and cardiac failure. A cyst of the pancreas was an incidental finding at necropsy. Grossly, the cyst was seen to be thin walled and located in the tail of the pancreas. On section clear serous fluid escaped. Microscopically, the cyst wall was observed to be made up of a delicate layer of connective tissue lined on the inside by a single layer of tall columnar epithelium. Immediately subjacent to the epithelial layer there were found at irregular intervals mucinous glands similar in appearance to Brunner's glands. Similar glandular structures were found also in the pancreas away from the cyst (fig. 5).

Cases reported in the literature and our own cases show that pancreatic cyst is usually a benign lesion. This, however, does not prove that the cyst may not be a precursor of carcinoma. The following case shows that carcinoma may develop secondary to cystic degeneration. It even seems possible that in some cases the rare primary adenocarcinoma of the pancreas develops on the basis of cystadenoma or pseudocyst of the pancreas. It is doubtful, however, whether this justifies calling cyst of the pancreas a precancerous lesion.

CASE 17.—S. S., a 69 year old woman, was admitted to the hospital because of itchiness of the skin, abdominal distress and loss of weight. She dated the

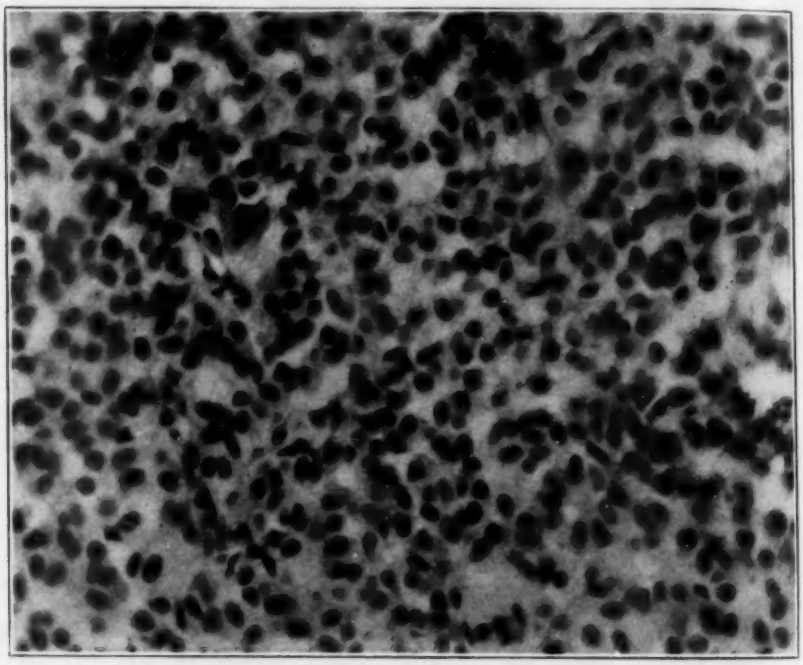

Fig. 6.—Photomicrograph showing pseudocyst of the pancreas with carcinomatous degeneration. Section shows sheets of tall cylindric cells occasionally grouped around a central lumen. There are few mitotic figures.

onset of her illness to six months previously, when she first complained of fulness in the epigastrium and nausea after eating. This lasted for a month, and the condition subsided. Two months later a heavy sensation in the epigastrium after eating again developed and was relieved by vomiting. Two months before admission the urine was turning dark in color; the stools were clay colored, and the patient became jaundiced. She was known to have diabetes for the last four years before admission, which was well conrtolled by diet. A lump had been felt in the epigastriunm for the last two years; it had been gradually increasing in size in recent months.

On examination the patient was jaundiced and emaciated. The abdomen presented a tender freely movable mass just to the right of the epigastrium which extended as far as the umbilicus and posteriorly toward the spine. Roentgen examination revealed that there was a deviation of the pylorus and a marked increase in the duodenal sweep with a narrowing of the lumen of the duodenum. It was suggested that the duodenal sweep embraced a tumor in the head of the pancreas. There was some obstruction to the outflow of barium sulfate from the stomach. The blood sugar varied between 100 and 276 mg. per hundred cubic centimeters; the icteric index was 111. The clinical diagnosis was carcinoma of the head of the pancreas.

At operation performed by one of us (J. R.) a large retroperitoneal cystic mass about 20 cm. in diameter was found to be located in the region of the head of the pancreas. Numerous dilated veins coursed over the free surface of the tumor. The gallbladder was thick walled and distended with thick dark bile; it was free of calculi. The wall of the cyst was incised, and about 2,000 cc. of sanguineous fluid was aspirated. In the belief that this was a pseudocyst of the pancreas, the cyst wall was marsupialized after a small portion had been removed for pathologic examination.

Biopsy showed the cyst wall to consist of sheets and nests of tall cylindric epithelium which varied somewhat in shape, size and staining characteristics. The nuclei were spherical or ovoid and in places vesicular and hyperchromatic. There were relatively few mitotic figures. In places the cells were grouped around a central lumen, simulating glandular formation. The cytoplasm of the cells was abundant and granular. The stroma was scant and composed of hyalinizing connective tissue enclosing thin-walled engorged blood vessels and a small number of round cells (fig. 6).

COMMENT

The clinical picture presented by this group of cases of pancreatic cyst merits some detailed description, though in many respects the cysts followed the pattern previously described by many authors. The diagnosis of these tumors is beset at times with many difficulties. The early symptoms and signs are by themselves not distinctive and are similar to those associated with other intra-abdominal lesions. In certain cases the difficulties in arriving at a diagnosis may appear insurmountable. The laboratory tests, although of great value, are by no means infallible.

Table 2 summarizes the salient data of our cases. Analysis of the diagnostic facts relating to this disease shows that pain is the most important subjective symptom. It was present in all of the operative cases, and varied from a sensation of fulness to sharp abdominal cramps. The location of the pain varied. In 6 patients the pain was localized in the epigastrium; in 2, in the lower part of the abdomen; in 1, in the left upper quadrant of the abdomen, and in the remaining patients the pain was diffuse throughout the abdomen. In many instances the pain was associated with nausea and vomiting.

Loss of weight occurred in 6 of the patients operated on; constipation, in 5, and diarrhea, in 2. Jaundice occurred in 3 patients. Of

TABLE 2.—*Summary of Salient Data of Seventeen Cases of Pancreatic Cyst*

Case	Age and Sex of Patient	Duration of Symptoms	Symptoms	Jaundice	Constipation	Diarrhea	Loss of Weight	Nutrition	Location of Mass	Preoperative Diagnosis	Postoperative Diagnosis	Chemical Composition of Cystic Fluid
1	56 ♀	3 yr.	Cramps	No	No	No	Yes	Emaciated	Pelvis	Retroperitoneal tumor	Pseudocyst of pancreas	Mucus, diastase and trypsin
2	35 ♀	6 mo.	Pressure in epigastrium; vomiting	No	No	No	Yes	Good	Left hypogastrium	Omental or pancreatic cyst	Pseudocyst	Not determined
3	47 ♀	2 weeks	Abdominal pain; vomiting	No	No	No	Yes	Good	None	Pancreatic tumor	Pseudocyst	Trypsin and fat
4	21 ♀	6 mo.	Enlarging abdomen	No	Yes	No	No	Good	Left side of abdomen	Cyst of ovary	Pseudocyst	Amylase
5	23 ♀	5 days	Epigastric distress; vomiting	No	Yes	No	No	Good	Left upper quadrant of abdomen	Chronic appendicitis	Pseudocyst	Amylase
6	31 ♀	8 mo.	Pain in left upper quadrant of abdomen	No	No	Yes	No	Good	Right upper quadrant of abdomen	Cyst of pancreas	Pseudocyst	Amylase
7	41 ♀	6 mo.	Abdominal pain	No	No	No	No	Obese	None	Cyst of pancreas; retroperitoneal sarcoma	Pseudocyst	Amylase and trypsin
8	49 ♀	5 mo.	Pain in left upper quadrant of abdomen	No	Yes	No	Yes	Obese	Right upper quadrant of abdomen	Cyst of pancreas	Pseudocyst	Amylase and lipase
9	23 ♀	3 mo.	Fulness in epigastrium	No	Yes	No	No	Good	Pelvis	Acute pancreatitis	Pseudocyst	Amylase and blood
10	48 ♀	4 mo.	Acute abdominal pain; vomiting	Yes	No	No	No	Good	None	Acute cholecystitis	Pseudocyst	Amylase, lipase and bile
11	72 ♀	6 weeks	Abdominal pain	Yes	No	No	Yes	Good	Left upper quadrant of abdomen	Carcinoma of pancreas	Pseudocyst	Not determined
12	28 ♂	2 days	Pain in lower part of abdomen; blood in stools	No	No	No	No	Good	None	Peptic ulcer	Cystadenoma of pancreas; duodenal ulcer	Not determined
13	45 ♀	5 mo.	Epigastric distress	No	No	No	No	Good	Left upper quadrant of abdomen	Cyst of pancreas	Cystadenoma of pancreas	Amylase
14	70 ♀	.....	Asthma	No	No	No	No	.....	None	Arteriosclerosis	Retention cyst	Not determined
15	76 ♂	.....	Coronary thrombosis	No	No	No	No	.....	None	Coronary thrombosis	Retention cysts	Not determined
16	42 ♂	.....	Cardiac failure	No	No	No	No	Good	None	Cardiac failure	Inclusion cyst of pancreas	Not determined
17	50 ♂	3 mo.	Dyspepsia	Yes	Yes	Yes	Yes	Emaciated	Right upper	Carcinoma of	Cyst	Blood, pus

121 cases reported by Körte, jaundice occurred in 9. Two of the patients with jaundice in our series had attacks of acute cholecystitis shortly before the discovery of the pancreatic cyst; the third patient with jaundice had a cyst of the head of the pancreas with carcinomatous degeneration.

Practically all the patients operated on presented past histories which may have had bearing on their illness. Thus they all experienced transient attacks of pain which varied in duration from two days to three years; the average duration of symptoms was about six months. Since trauma, cholecystitis and pancreatitis are frequently associated with formation of cyst of the pancreas, these must be considered in evaluating the symptoms of this disease. Two of the patients in this series had attacks of cholecystitis, and 1 had an attack of acute pancreatitis before the cyst developed in the pancreas. None of the patients, however, gave a history of trauma prior to the onset of illness. Three of the patients felt a gradually increasing swelling in the abdomen; in 1 instance the swelling was felt for two years, and at operation the lesion proved to be a pseudocyst with carcinomatous degeneration. In the group of cases in which operation was not done, the cysts were small and yielded no clinical evidence of their presence.

Physical examination revealed that 10 patients were well nourished, that 2 were obese and that 2 were emaciated. Only 3 patients appeared acutely ill on entering the hospital. Tenderness over the affected area was elicited in 5 patients.

Pseudocystic tumor usually presented itself as a large semifluctuant mass. In 4 cases it was located in the left upper quadrant of the abdomen; in 3, in the right upper quadrant of the abdomen; in 2, in the lower part of the abdomen, and in 1 case the mass occupied the entire left side of the abdomen. A mass was felt in 114 of the 121 cases which Körte reviewed from the literature. In 45 of the 47 cases reported by Judd, Mattson and Mahorner,[8] more than 95 per cent, the tumor was felt above the umbilicus. In 21 cases the tumor was to the left of the median line; in 11, approximately in the median line, and in 13, to the right of the median line. In 1 case the tumor was felt in the pelvis and was found enclosed in the mesentery of the sigmoid.

Cysts of the pancreas as a rule are relatively immobile. They are more apt to be freely movable when situated in the tail of the organ. Mobility of the cyst was noted in 6 cases of the present series; in 3 the cyst was described as ballotable, and in 3 others it was said to be moving freely with respiration.

8. Judd, E. S.; Mattson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of Forty-Seven Cases, Arch. Surg. **22**:838 (May) 1931.

Roentgen examination is a major aid in the diagnosis of cyst of the pancreas. An enlarged duodenal curve is characteristic of enlargement in the region of the head of the pancreas. So too, displacement of the duodenum and the small intestine points toward the diagnosis of cyst of the pancreas. In 6 of the patients, roentgen examination revealed the presence of a mass in the region of the pancreas. When the head of the pancreas was the seat of the tumor, definite changes in the angle of the duodenum were observed.

The preoperative diagnosis was cyst of the pancreas in 4 cases, carcinoma of the pancreas in 2, retroperitoneal tumor in 1, omental or pancreatic cyst in 1, ovarian cyst or fibromyoma of the uterus in 1, peptic ulcer in 1, acute pancreatitis in 1, acute cholecystitis in 1, chronic appendicitis in 1 and retroperitoneal sarcoma or cyst of the pancreas in 1.

The pathologic picture presented at operation is characteristic. The large cyst arising from the region of the pancreas is so striking that one can scarcely fail to diagnose the condition at operation after having once viewed the lesion. The tumor usually presents itself as a smooth, relatively immobile, hemispheric and semifluctuant swelling, arising in the region of the pancreas. On aspiration, it yields a sanguineous fluid. One of the cysts in the series had globules of oil in addition to blood, and another showed the presence of bile. The size of the tumor in this series varied from 5 to 30 cm. in diameter. In 3 instances the tumor extended into the pelvis and contained several liters of fluid.

The existence of pancreatic secretions in the cyst has been frequently noted. On the other hand, numerous instances of true cysts are on record in which no ferments were found. To confirm or exclude the diagnosis of pancreatic cyst, the absence of ferments therefore appears to be of relatively little value. Chemical analysis of the aspirated fluid in our series revealed that 10 of the examined specimens showed the presence of trypsin, amylase or both. In 6 instances no chemical analysis was done, and in the case of pseudocyst with carcinomatous changes no enzymes could be found in the aspirated fluid. Some of the cysts also contained mucus, fat, bile and lipase.

The histologic descriptions in the literature are similar to those in our cases. It seems unnecessary to repeat the histologic picture in detail, but a few points might be reemphasized. In the cases of pseudocyst, the wall was made up almost entirely of dense layers of fibrous connective tissue lined on the inner surface with a single layer of cuboid epithelium. In many instances an epithelial covering was entirely absent. At no time was there found pancreatic tissue in the wall of the cyst, thus indicating that the origin of the cyst was probably extrapancreatic (fig. 2).

Cystadenoma represents the true form of pancreatic tumor. This type of neoplasm is not common; it occurred in 2 cases of the present

series. The lesion was characterized by a rich papillary formation arising from the inner lining of the cyst. Each papilla was composed of a thin stalk of fibrous tissue lined by one or several layers of epithelial cells (fig. 3).

Retention cyst of the pancreas is in all probability a result of some form of obstruction to the pancreatic duct. In the cases cited the cyst wall was thin and lined by a single layer of cuboid or flat epithelium (fig. 4).

Inclusion cysts develop in the pancreas from cells which are not normally there but which were incorporated in the organ from some extraneous tissue by a faulty development in embryonal life. Slight flaws in the embryologic development, which are frequent, would be sufficient to explain the possibility of retention of Brunner's glands in the adult pancreas. This hypothesis also explains the similarity between the glands found in the pancreas to those of Brunner's glands. These glands are enclosed within the pancreas, and the formation of cysts may occur because the epithelium is found to be secreting. Their great rarity makes it improbable that every pancreas under certain circumstances harbors these glands. In the case reported here the cyst was lined by tall columnar epithelium similar in appearance to the cells lining Brunner's glands. In addition there were found in the pancreas mucinous glands of the Brunner type both in the immediate vicinity of the cyst and at some distance from it (fig. 5).

Pseudocyst of the pancreas with carcinomatous degeneration is of rare occurrence. Mahorner and Mattson[9] reported 4 cases of carcinomatous cyst among 88 patients with pancreatic cyst treated surgically at the Mayo Clinic. It occurred in 1 case in our series. The tumor is usually slow growing, and, as far as our knowledge goes, metastases have not been observed even when a large primary tumor was present for a long time. The tumor reported was apparently present for two years before the patient sought medical advice. Microscopic examination of the cyst showed it to be a relatively slow growing neoplasm (fig. 6).

Choice of operation depends on the size, the variety, the situation and the condition of the cyst. The ideal treatment is complete removal, if possible. Small cysts, especially when in the tail of the pancreas, should be excised. In cases in which the cyst is large and adherent, marsupialization of the tumor is the method of choice.

Little need be said of the prognosis in cases of pancreatic cyst. Benign cystic growths can be removed with only a slight mortality rate, whereas malignant tumors in the pancreas, like those in other locations, permit only a poor prognosis.

9. Mahorner, H. R., and Mattson, H.: Etiology and Pathology of Cysts of Pancreas, Arch. Surg. **22**:1018 (June) 1931.

SUMMARY

Seventeen cases of primary cyst of the pancreas are reviewed. In 11 of these the lesion was pseudocyst; in 2, cystadenoma; in 2, retention cyst; in 1, inclusion cyst, and in 1, pseudocyst with carcinomatous degeneration.

The diagnosis of pancreatic cysts is difficult at times, but, given a large cystic mass extrinsic to the gastrointestinal tract, the possibility of cyst should be borne in mind. Roentgen examination is of considerable help in making a diagnosis.

The presence or absence of pancreatic enzymes in the cyst fluid is not pathognomonic of the disease.

From the embryologic point of view it is conceivable that certain pancreatic cysts may arise from misplaced remnants of Brunner's glands. Such a tumor is described in 1 of the cases presented.

781 Ocean Avenue.

25 Eastern Parkway.

POSTOPERATIVE CHYLOTHORAX

SUDDEN DEATH FOLLOWING THE INFUSION OF ASPIRATED CHYLE

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AND
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Within the year an excellent article on traumatic chylothorax appeared in this journal.[1] A cure was effected by the intravenous administration of the aspirated chyle. In contradistinction the present paper reports a case of postoperative chylothorax in which sudden death followed such intravenous administration of chyle. Our article further stresses: (1) the rarity of such a lesion; (2) the dangers of inadvertent section of the duct during sympathectomy operations for hypertension; (3) the precautions to be taken following such a mishap, and (4) the possible cause of such sudden death.

LITERATURE

This is the first case to be reported of inadvertent sectioning of the thoracic duct during the course of a sympathectomy operation. It is the second case to be reported of such sectioning during the course of any operation. Indeed, chylothorax from any trauma is a rare condition. Shackelford and Fisher [2] collected 43 authentic cases. Nowak and Barton,[3] Smith and Woliver,[1] Dorsey and Morris [4] and Little, Harrison and Blalock [5] each added another case. In the majority of cases the condition was caused by injuries within the lower part of the thoracic cage. The mortality rate averaged 50 per cent in the total series.

From Hartford Hospital.

1. Smith, D. D., and Woliver, E.: Traumatic Chylothorax, Arch. Surg. **43**: 627-632 (Oct.) 1941.

2. Shackelford, R. T., and Fisher, A. M.: Traumatic Chylothorax, South. M. J. **31**:766-775 (July) 1938.

3. Nowak, S. J. G., and Barton, P. N.: Chylothorax, J. Thoracic Surg. **10**: 628-634 (Aug.) 1941.

4. Dorsey, J. F., and Morris, C. G.: Traumatic Rupture of the Thoracic Duct with Chylothorax, J. A. M. A. **119**:337-338 (May 23) 1942.

5. Little, J. M.; Harrison, C., and Blalock, A.: Chylothorax and Chyloperitoneum, Surgery **11**:392-401 (March) 1942.

There have been only 5 cases [6] in which treatment consisted of intravenous injection of the aspirated chyle. Two patients died; 2 recovered, and 1 remained in status quo. In 1908 Oeken [6a] first reported the use of this method with a fatal result. In 1937 Bauersfeld [6b] first cured 1 patient by the direct transfer of intrathoracic chyle into the basilic vein. In this journal in October 1941, Smith and Woliver [1] recorded another case in which treatment by four indirect transfusions of chyle of approximately 750 to 1,000 cc. each was successfully carried out. The chyle was collected in citrate, cultured for sterility and refrigerated for twenty-four hours or longer. Since then Dorsey and Morris [4] have reported a case in which the patient died despite the infusion of chyle. Little, Harrison and Blalock [5] recently published a comprehensive report of a case in which combined chylothorax and chyloperitoneum developed in a 17 year old girl, probably secondary to traumatic thrombophlebitis of the left internal jugular vein. At the time of the report (March 1942) the phenomenal total of approximately 540 liters of chyle had been removed over a period of eighteen months by peritoneal and left pleural taps. This constituted an average of 1,000 cc. a day. Approximately 22,500 cc. of this chyle was reinfused over the first six month period. None was reinfused over the ensuing twelve month period. The authors noted no improvement following the chylous transfusions. At the time of writing the patient was still alive.

SIGNS AND SYMPTOMS

In all cases of chylothorax, whether traumatic, operative or spontaneous, there are: (1) a history of delayed onset, generally from the seventh to the tenth day following the known severance; (2) a rather sudden onset of dyspnea; (3) continuing respiratory embarrassment with mild shock; (4) massive intrathoracic chyle (as much as 3,500 cc.), generally on the right side; (5) the necessity for frequent thoracenteses (as often as twice daily); (6) spontaneous healing and sealing of the severed duct in from seven to twenty-one days, provided the patient survives (Little's case [5] is in contradistinction to this); (7) emaciation from the lowering of serum protein and to a lesser extent of the serum lipoids; (8) a 50 per cent mortality rate from inanition rather than respiratory embarrassment.

FUNCTION

The thoracic duct starts just anterior to the second lumbar vertebra and passes through the aortic hiatus of the diaphragm just anterior and

6. (*a*) Oeken: Ein Fall von Zerreissung des Ductus thoracicus infolge Brustquetschung, München. med. Wchnschr. **55**:1182-1183, 1908. (*b*) Bauersfeld, E. H.: Traumatic Chylothorax from Ruptured Thoracic Duct Treated by Intravenous Injection of Aspirated Chyle, J. A. M. A. **109**:16-18 (July 3) 1937. (*c*) Shackelford and Fisher.[2] (*d*) Dorsey and Morris.[4] (*e*) Little, Harrison and Blalock.[5]

to the right of the aorta. In ascending the thorax it slowly shifts to the left, ultimately joining the left subclavian vein. This course shows some variation in 27 per cent of the cases.[7] Sixty per cent of the digested fat passes through this duct with as much as 130 to 195 cc. of chyle entering the veins of the neck each hour. The protein content ranges from 1 to 6 Gm. per hundred cubic centimeters. The fat content varies from 0.4 to 2.8 cc. per hundred cubic centimeters. The chyle is alkaline in reaction and contains a high percentage of lymphocytes. In cases of chylothorax there is a consequent decrease of lymphocytes in the circulating blood. On settling the chyle has three layers: a cream layer on top, a milk layer in between and a cellular sediment layer on the bottom. In most of the cases it has been reported as sterile.

The treatment of chylothorax is aimed at satisfying two chief requirements: (1) the prevention of respiratory embarrassment and (2) the maintenance of nutrition. Only enough chyle has been removed to permit adequate respiratory function. Further removal apparently stimulates further leakage. Refeeding of the aspirated chyle by mouth has not been of benefit. In recent years the chyle has been replaced, first by direct[8] and then by indirect infusions.[9] In the case of Smith and Woliver the aspirated citrated chyle was allowed to stand from one to four days before use. No harmful reactions were noted. Nowak,[10] in Boston, has used this same method in experimental work on dogs and has advised the use of such a method in clinical practice. The intravenous administration of heterogenous fats emulsified by the Yamakawa method has been used in pediatric practice by Holt and associates[11] without reactions. Gildea[12] has had 1 severe reaction but no fatality (with its use in the treatment of psychiatric patients).

There is general agreement that no attempt should be made to reoperate in an effort to repair the duct. Exposure is most difficult.

REPORT OF CASE

A. T. P., a 39 year old small, almost emaciated, woman, was admitted to Hartford Hospital on Aug. 28, 1941, because of precordial pain, nervousness, weakness and underweight. She weighed only 89 pounds (40.4 Kg.) and on examination was found to have grade 2 essential hypertension with a blood pressure of 210 systolic and 140 diastolic. Nonprotein nitrogen, basal metabolic rate, intra-

7. Davis, H. K.: A Statistical Study of the Thoracic Duct in Man, Am. J. Anat. **17**:211-244, 1914.

8. Little, Harrison and Blalock.[5] Bauersfeld.[6b]

9. Smith and Woliver.[1] Bauersfeld.[6b]

10. Nowak, S. J. G.: Personal communication to the authors.

11. Holt, L. E., Jr.; Tidwell, H. C., and Scott, T. F. McN.: The Intravenous Administration of Fat, J. Pediat. **6**:151-160 (Feb.) 1935.

12. Gildea, E. F.: Personal communication to the authors.

venous pyelogram, cardiac outline, chest plate, gastric analysis, blood, urine and stool analyses were all normal. She exhibited signs of grade 2 hypertensive retinopathy (Wagener and Keith classification) and showed an excellent fall in blood pressure (to 120 systolic and 90 diastolic) following the various sedative tests. She was deemed a good candidate for transdiaphragmatic sympathectomy to be done in two stages according to the method of Smithwick.[13]

On October 20 sympathectomy was done on the right side. After the twelfth rib was removed and the diaphragm was split, the right splanchnic nerves as well as the chain were visualized and resected from approximately the tenth dorsal down to and including the second lumbar sympathetic ganglion.

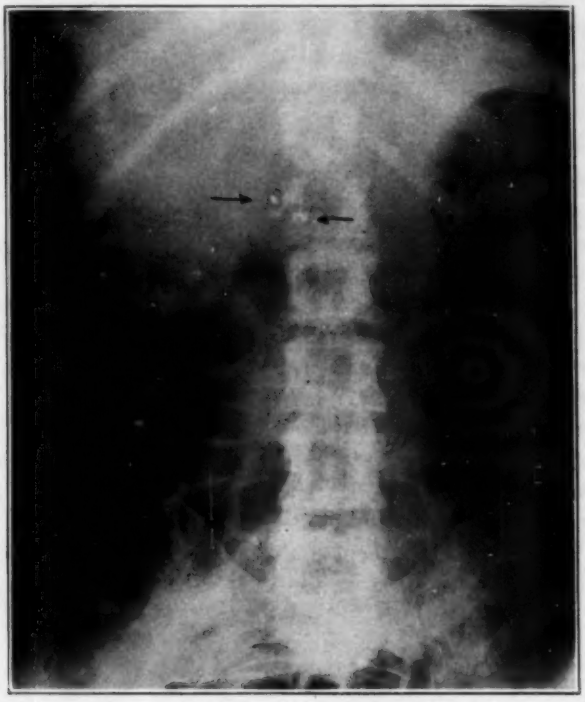

Fig. 1.—Roentgenogram showing the location of clips on cut ends of the thoracic duct.

At operation the extraordinary emaciation of this patient was noted. The entire posterior and lateral surfaces of the aorta and the anterior surface of the vertebral bodies could be easily visualized. In an effort to remove the aortic and lesser branches of the splanchnic nerve the thoracic duct at the level of the first lumbar vertebra was exposed and inadvertently torn. The duct was promptly recognized as such. No attempt was made to suture it, but it was doubly clipped with two silver clips placed tightly on both the distal and the proximal end (fig. 1). A small portion was examined microscopically; this proved it to be a tube lined with epithelial cells.

13. Smithwick, R. A.: A Technique for Splanchnic Resection for Hypertension. Surgery **7**:1-8 (Jan.) 1940.

The operation was concluded without complications. The early convalescence was uneventful with a blood pressure of 140 systolic and 90 diastolic. But at the end of one week the patient looked worse, and some respiratory embarrassment had developed. A chest film revealed a small amount of fluid at the base of the right lung. On the fourteenth postoperative day the patient experienced a sudden onset of severe dyspnea and cyanosis and exhibited flatness over the entire right side of the chest, with complete opacity to roentgen rays (fig. 2); 2,150 cc. of cream-colored pinkish fluid was removed by thoracentesis. It coagulated on standing. A direct smear showed many white blood cells with 80 per cent lymphocytes as well as fat globules by sudan III stain. No bacteria were seen on smear or

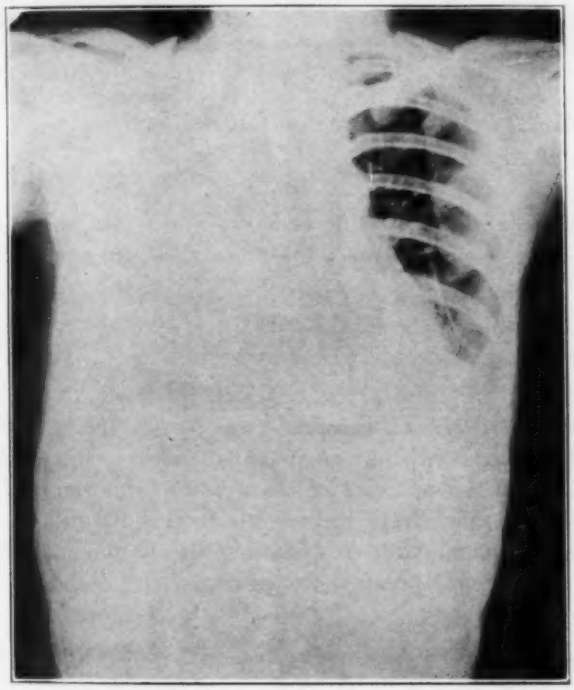

Fig. 2.—Roentgenogram of the thorax taken on the fourteenth postoperative day, showing complete obliteration of the right lung filled by chyle.

culture. A repeat thoracentesis on the sixteenth postoperative day yielded 1,500 cc. of chyle. The patient's general condition was bad; she was considerably weakened. The serum protein had dropped to 5 Gm. per hundred cubic centimeters and the white blood cell count to 3,500 with a decrease chiefly of lymphocytes. On the seventeenth postoperative day 1,500 cc. of additional chyle was aspirated. The patient became weaker, and the serum protein fell alarmingly to 3.8 Gm. per hundred cubic centimeters with a blood calcium content of 7.9 mg. per hundred cubic centimeters. Transfusions of blood and plasma on the sixteenth and seventeenth days caused general improvement and a rise in the serum protein content to 4.3 Gm. per hundred cubic centimeters.

In line with the work of Bauersfeld [6b] and Smith and Woliver [1] as well as the verbal advice of Nowak [10] it was decided to replace the aspirated chyle by a delayed citrated infusion. Eight hundred and fifty cubic centimeters of chyle was aspirated aseptically by the closed method in a citrated blood transfusion outfit. It was placed in a refrigerator, and a sample was taken for culture which proved sterile after twenty-four hours. The chyle was then given fractionally by the gravity method. Ten cubic centimeters was first given slowly in solution of sodium chloride without reaction; following this administration of the main amount was started slowly at the rate of approximately 200 cc. per hour. After 75 cc. had run in, a chill developed. The infusion was immediately stopped, but the chill grew worse and was accompanied by true asthmatic breathing, generalized shock and a sense of impending death. The patient was placed in extreme shock position; her legs were elevated and bandaged with elastica bandages. Epinephrine was given intravenously. She experienced temporary relief, especially from the asthmatic breathing and the cyanosis. In a few minutes, however, the asthma returned. She again became cyanotic and gasping and died, notwithstanding the administration of more epinephrine. Permission for autopsy was refused.

COMMENT

This presentation of a tragic series of mishaps culminating in death is presented because of the following unusual features:

1. For the first time in our experience, as well as in the voluminous sympathetic literature, the thoracic duct was exposed and inadvertently torn while sympathectomy was being done for hypertension. The patient's extreme emaciation made her vulnerable.

2. Delayed chylothorax occurred even though the thoracic duct had been doubly closed with four silver clips, two on either end (fig. 1). In all probability the pressure of chyle within this duct is far greater than one would expect from the experimental work of Mouchet [14] and Blalock, Cunningham and Robinson.[15] Consequently either from erosion or from simple pressure the proximal end reopened at approximately seven to ten days.

3. Extreme caution and care must be exercised if intravenous administration of chyle is to be used. This patient died promptly from what appeared to be anaphylactic shock. She exhibited asthma, dyspnea, cyanosis, chills and shock momentarily improved by epinephrine and occurring within minutes of the start of infusion. Without autopsy it is impossible to differentiate conclusively between anaphylaxis, fat embolism and a foreign protein reaction. The clinical picture is most suggestive of the first. In 1 previous fatal case the patient also died suddenly after

14. Mouchet, A.: Le chylothorax traumatique, J. de chir. **42**:386-399 (Sept.) 1933.

15. Blalock, A.; Cunningham, R. S., and Robinson, C. S.: Experimental Production of Chylothorax by Occlusion of Superior Vena Cava, Ann. Surg. **104**:359-364 (Sept.) 1936.

the infusion of autogenous chyle [6a] and at autopsy showed diffuse hemorrhagic exudate over the viscera and asphyxia, suggesting anaphylaxis. The other more recently reported death [4] was apparently due to inanition. Of the 6 cases in the literature in which this therapy was administered, death occurred in 3.

Necessary precautions in the future will consist of: (1) a careful test for sensitivity followed by a slow administration of 5 to 10 cc. intravenously and a delay of thirty minutes before starting the infusion proper; (2) microscopic measurements of the size of the fat globules with rejection of specimens containing globules of a diameter over 3 microns; [11] (3) twenty-four hour culture of the chyle (Little and associates [5] recommended direct infusion using a closed system with a three way stopcock); (4) in cases in which the chyle fails to meet the aforementioned standards, the intravenous use of plasma and of emulsified fats [11] with daily aspiration of the chyle; (5) in cases in which chylothorax persists after one week of this regimen, phrenicectomy as reported by Nowak and Barton; [8] (6) intravenous infusion of fat and protein to be done at an early date to prevent rapidly progressive emaciation.

SUMMARY

A review is made of the literature on chylothorax.

A report is presented of a case of chylothorax following sympathectomy for hypertension. Sudden death followed the intravenous administration of autogenous chyle in this case.

Precautions against the future occurrence of death are listed and methods of therapy are suggested.

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SODIUM SALTS OF THE SULFONAMIDE COMPOUNDS

A STUDY WITH SPECIAL REFERENCE TO THEIR LOCAL USE IN WOUNDS

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At present sulfanilamide is the accepted sulfonamide compound for local use in war wounds, compound fractures and the peritoneum.[1] Experiments in vitro, however, have clearly shown that sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) are more potent antibacterial agents than sulfanilamide and are also far more resistant to drug inhibitors, such as paraaminobenzoic acid.[2] Actually, against Escherichia coli (frequently a participant in peritonitis following intra-abdominal wounds) 1 mg. of sulfathiazole or sulfadiazine can accomplish as much as 430 mg. of sulfanilamide. To obtain bacteriostasis, furthermore, in the presence of 1 mg. per hundred cubic centimeters of paraaminobenzoic acid (or similar inhibitor of drug action) 15 mg. per hundred cubic centimeters of sulfadiazine or sulfathiazole is required, whereas 6,280 mg. per hundred cubic centimeters of sulfanilamide is necessary! Clinical experience has also demonstrated the superiority of these newer drugs over sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine).[3] Nevertheless, these drugs have not supplanted sulfanilamide in local therapy. Why?

It has been assumed that the relatively high water solubility of sulfanilamide facilitates its ready penetration and spread throughout

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The drugs used in this study were provided by the Lederle Laboratories, Inc.

From the Department of Bacteriology, Columbia University College of Physicians and Surgeons.

1. Cloward, R. B.: War Injuries to the Head, J. A. M. A. **118**:267 (Jan. 24) 1942. Veal, J. R., and Klepser, R. G.: Local Use of Sulfanilamide Therapy in Surgical Infections, Surgery **10**:947 (Dec.) 1941.

2. Rose, H. M., and Fox, C. L., Jr.: A Quantitative Analysis of Sulfonamide Bacteriostasis, Science **95**:412 (April 17) 1942.

3. Long, P. H.: Sulfadiazine: 2-Sulfanilamidopyrimidine Analogue of Sulfanilamide, J. A. M. A. **116**:2399 (May) 1941. Trevett, G. I.; Nelson, R. A., and Long, P. H.: Studies on Sulfadiazine: II. Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections, Other Than Pneumonia, Bull. Johns Hopkins Hosp. **69**:303 (Oct.) 1941.

the local area resulting in its rapid absorption into the circulation. Bick, however, reported that sulfanilamide itself when placed in wounds is not completely dissolved and absorbed and may act somewhat as a foreign body in delaying healing.[4] The poor water solubility, on the other hand, of sulfadiazine and sulfathiazole has made them appear unsuited for this purpose. Many observers have in fact reported on the poor absorption of these drugs following implantation in the rectus muscle[5] and in wounds.[6] Subsequently, Taylor[7] reported that three days after implantation of sulfathiazole and sulfadiazine "actual abscesses were formed about crystals which still persisted in the tissues." It seemed important, therefore, to study the properties of the soluble sodium salts of sulfathiazole and sulfadiazine to assess their suitability for local use in wounds and in the peritoneum to obtain the benefits of these superior, more effective antibacterial agents. It will be shown by actual experimentation that these salts are suitable for local use in wounds.

It seemed likely that this study might suggest also a means of preventing a not uncommon complication of chemotherapy, viz., renal precipitation of the free and acetylated drugs. This disadvantage has been associated with the relatively poor water solubility of sulfapyridine, sulfathiazole and sulfadiazine and has to some extent limited the systemic use of these potent chemotherapeutic agents. In view of the fact that when ionized (as are the sodium salts) their solubility is greatly increased, investigation of the physiologic possibility of inducing urinary excretion of these drugs in the form of their soluble salts might yield a method of preventing precipitation of these drugs in the kidney.[8]

COMPARATIVE ALKALINITY OF SOLUTIONS OF THE SODIUM SALTS OF THE SULFONAMIDE COMPOUNDS

Because of the not infrequent earlier experience that the extremely alkaline sodium sulfapyridine when allowed to leak under the skin during intravenous injection produced necrosis of the tissues followed

4. Bick, E. M.: Topical Use of Sulfonamide Derivatives, J. A. M. A. **118**:511 (Feb. 14) 1942.

5. Long, P. H.: Clinical Use of Sulfonamide Compounds in Prophylaxis and Treatment of Infections, Northwest Med. **40**:311 (Sept.) 1941.

6. Hawking, F., and Piercy, J. E.: Blood Concentrations Following Local Applications of Sulfonamide Compounds to Wounds, Brit. M. J. **1**:511, 1941.

7. Taylor, F. W.: Misuse of Sulfonamide Compounds, J. A. M. A. **118**:955 (March 21) 1942.

8. Jensen, O., and Fox, C. L., Jr.: Factors Controlling Absorption and Renal Excretion of Sulfadiazine, to be published.

by sloughing, it has been supposed that sodium sulfathiazole (the sodium salt of 2-[paraaminobenzenesulfonamido]-pyridine) and sodium sulfadiazine (the sodium salt of 2-[paraaminobenzenesulfonamido]-pyrimidine) would do the same. Actually this is not the case. There are also numerous references in the literature to the high alkalinity of these sodium salts. For example, 10 per cent solution of sodium sulfathiazole has been assigned "p_H 10 to 11" and compared to 10 per cent solution of sodium hydroxide.[9] Because of "hydrogen ion concentration of approximately 10 to 11" these drugs have also been described as "irritating to an already sick peritoneum."[10] My measurements give much lower values. The p_H, for example, of 1 per cent solution of sodium sulfadiazine (twenty-fifth molar) is 8.66, and an equimolar solution of sodium bicarbonate has a p_H of 8.7 (table 1 and chart 1).

TABLE 1.—*Comparative Alkalinity of Solutions of the Sodium Salts of Sulfonamide Compounds*

Concentration of Solution	p_H of Aqueous Solutions of the Sodium Salt of			
	Sulfapyridine	Sulfathiazole	Sulfadiazine	Carbonic Acid *
5.0 per cent	10.6	9.8	9.4	
2.5 per cent	10.3	9.6	9.3	
1.0 per cent	10.1	9.4	8.7	8.7
0.5 per cent	10.0	9.1	8.4	8.7
0.2 per cent (200 mg. per 100 cc.)	9.8	9.0	7.9	
100 mg. per 100 cc.	9.7	8.7	7.6	
50 mg. per 100 cc.	9.4	8.4	7.5	
10 mg. per 100 cc.	8.4	8.0	7.3	

* The solution of a sodium salt of carbonic acid used was an equimolar solution of sodium bicarbonate exposed to air.

Furthermore, solutions of the sodium salts of these drugs, like bicarbonate, are buffered by tissue fluids to the p_H of the blood. Thus, sodium sulfathiazole added to normal human plasma in a concentration of 100 mg. per hundred cubic centimeters raised the p_H of normal human plasma 0.1 p_H unit. This same concentration of sodium sulfadiazine did not change the p_H of the plasma enough to register any increase with the sensitive glass electrode. Similar results were obtained with whole blood. In table 1 and chart 1 are comparisons of the alkalinity of

9. Fletcher, R.: The Caustic Action of Sodium Sulfathiazole, J. A. M. A. **117**: 1204 (Oct. 4) 1941; Application of Sulfonamide Compounds to the Nose, ibid. **118**: 998 (March 21) 1942. Reichert, F. L., in discussion on papers of Muller and Thompson and Jackson and Coller, J. A. M. A. **118**:200 (Jan. 17) 1942.

10. Province, W. D.: Sulfonamide Compounds—Their Uses and Principles of Therapy, J. Indiana M. A. **34**:659 (Dec.) 1941.

various solutions of the sodium salts of these drugs and of sodium bicarbonate. The results show that increasing the concentration of the drug from 1 to 5 per cent raises the p_H but slightly. Concentrations above 5 per cent are hypertonic and will be rapidly diluted by an influx of the tissue fluids.

In clinical practice at the Babies Hospital, New York, Dr. Gilbert M. Jorgenson demonstrated [11] that a 5 per cent aqueous solution of sodium sulfadiazine may be given subcutaneously (0.1 Gm. per kilogram of body weight) without clinical evidence of local tissue damage. More than forty hypodermoclyses were given; they were administered in the same subcutaneous area twice daily for more than one week. No local reaction was observed.

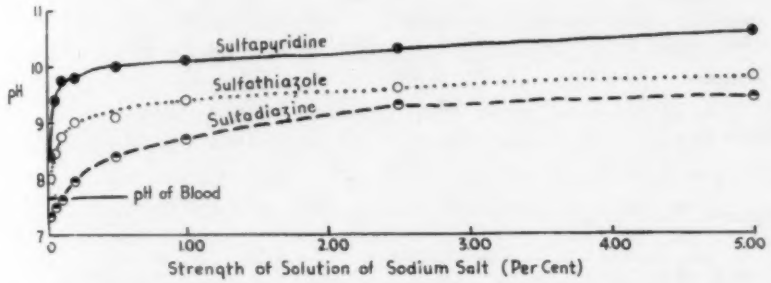

Chart 1.—The p_H of various strength solutions of the sodium salts of three derivatives of sulfanilamide.

DISSOCIATION OF THE SULFONAMIDE COMPOUNDS AND THE EFFECT OF THEIR IONIZATION ON THEIR SOLUBILITY

To obtain more complete comparative data, the dissociation constants of these drugs were measured. The p_K values obtained—that is the p_H [12] of an equimolar mixture of the drug (weak acid) and its soluble sodium salt—are given in table 2. Such data facilitate comparison of the relative acidity of these drugs and of other acids, e. g. carbonic and boric acids; these data are included in table 2 for comparison. The alkalinity of their sodium salts may likewise be gaged. Thus the most acidic drug, sulfadiazine, will have the least alkaline sodium salt. From these constants, furthermore, it is possible to estimate the relative amounts of each drug that exists in the ionized state at the p_H of biologic fluids (7.5). It is noteworthy (as shown in table 2) that in the body sulfa-

11. Jorgenson, G. M.: To be published.

12. All p_H measurements were made with the Beckmann glass electrode and vacuum tube potentiometer.

thiazole and sulfadiazine are almost completely ionized, whereas sulfanilamide is but slightly ionized. (The relation of this fact to the bacteriostatic potency of these drugs and to the effective blood level has been pointed out elsewhere.[13])

In view of the relative acidity of sulfadiazine it seemed likely that its low water solubility might be increased in a physiologic buffer, in

TABLE 2.—*Comparative Acidity of Sulfonamide Compounds and Degrees of Ionization at the Hydrogen Ion Concentration of Biologic Fluids* *

Drug (Acid)	Acidity (p_K)	Status at p_H 7.5: Ratio Ionized Salt / Nonionized Acid	Status at p_H 7.5: Percentage Ionized in Form of Salt
Sulfanilamide	10.55	1 / 1,120	0.1
Boric acid	9.2	.....	...
Sulfapyridine	8.5	1 / 10	9.1
Sulfathiazole	6.8	5 / 1	83.4
Carbonic acid	6.55	.....	...
Sulfadiazine	6.4	13 / 1	92.9

* Taken as p_H 7.5.

TABLE 3.—*Influence of Ionization on the Solubility of Sulfonamide Compounds*

Drug	Solubility in Water at 37 C., Mg. per 100 Cc.	Solubility in Fifteenth Molar Phosphate Buffer at 37 C., Mg. per 100 Cc.	Final p_H Attained	No. of Times Increase in Solubility in Phosphate Buffer
Sulfanilamide	1,400.0	1,720	7.30	1.2
Sulfaguanidine (sulfanilylguanidine)	190.0	235	7.42	1.2
Sulfapyridine	49.5	75	7.38	1.5
Sulfathiazole	94.0	248	7.36	2.6
Sulfadiazine	12.3	167	7.40	13.6

which it would exist in large proportions (table 2) as the extremely soluble ionized sodium salt. In these experiments a fifteenth molar phosphate buffer raised the solubility of sulfadiazine fourteenfold, as shown in table 3. Feinstone and associates[14] first reported on the

13. Fox, C. L., Jr., and Rose, H. M.: Ionization of Sulfonamides, Proc. Soc. Exper. Biol. & Med. **50**:142 (May) 1942.

14. Feinstone, W. H.; Williams, R. D.; Wolff, R. T.; Huntington, E., and Crossley, M. L.: Toxicity, Absorption and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine), Bull. Johns Hopkins Hosp. **47**:427 (Dec.) 1940.

increased solubility of these drugs in biologic fluids. They furthermore determined

> . . . that urea and sodium chloride are not responsible for the greatly increased solubility . . . Whether the apparent increase in solubility represents true solution or colloidal dispersion, especially in the blood, is not known, although it is believed that the latter possibility is rather remote.

In another study [15] the influence of dextrose and specific gravity was observed in an effort to explain this phenomenon. It is now apparent that these factors are insignificant and that the increased solubility in biologic fluids as in phosphate buffer must be largely, if not entirely, attributed to the formation of ionized soluble salts of these drug acids. In urine some solubility results from formation of soluble glucuronates.[16] These may arise secondarily from oxidation of the drugs in the body;[17] the hydroxyl derivatives then formed are subsequently conjugated with glucuronic acid. The significance of these data in relation to the absorption, the distribution and the excretion of this drug is at present under study.[8]

The important suggestion from these facts, however, is that since sulfadiazine and sulfathiazole occur in the body largely in the ionized form and since their sodium salts are only moderately alkaline, resembling sodium bicarbonate, the local use of these soluble salts seems to be worthy of trial.

EXPERIMENTS IN VIVO WITH SODIUM SALTS IN WOUNDS

Preliminary tests were carried out in mice and in dogs to determine whether the sodium salts are irritating to tissues and to ascertain the speed and the degree of their absorption into the general circulation.

White mice (weight, 20 Gm.) were anesthetized with ether; a 2 cm. incision was made into the muscles of the back, and 20, 40 or 50 mg. of the powdered sodium salts of sulfapyridine, sulfathiazole or sulfadiazine was placed in the pocket, which was then closed with black silk. The powder rapidly formed a uniform soft wet paste with the tissue fluid, some of the powder apparently dissolving quickly. There was no evidence of caking in the wound, and the time of healing was practically the same as in control mice. This is in marked contrast to similar

15. Curtis, A. C., and Sobin, S. S.: The Solubility of Acetyl-Sulfapyridine and Acetyl Sulfathiazole in the Urine, Ann. Int. Med. **15**:884 (Nov.) 1941.

16. Scudi, J. V.; Ratish, H. D., and Bullowa, J. G. M.: Increased Glucuronate Excretion Following Administration of Sulfapyridine, Science **89**:516 (June 2) 1939. Thorpe, W. V., and Williams, R. T.: Isolation of Acetylsulphathiazole from Human and Rabbit Urines Following Administration of M. & B. 760, Nature, London **146**:686 (Nov. 23) 1940.

17. Fox, C. L., Jr.: The Significance of the Oxidation of Sulfanilamide During Therapy, Am. J. M. Sc. **199**:487 (April) 1940.

experiments in which the acid forms of the drugs were used. The wounds in the mice that received sodium sulfapyridine showed a little more serous exudate than the controls; there was, however, no gross evidence of inflammatory reaction or necrosis. Microscopic sections taken eighteen hours after implantation showed disappearance of the drug with no chemical necrosis. A moderate degree of edema was present both in the control mice that received no drug and in the treated animals. The polymorphonuclear infiltration was but slightly less in the sections of the control mice. It should be noted that in these experiments the amounts of drug used represented doses of 70 to 150 Gm. in man.

These results were encouraging; but for comparison with Long's experiments [5] showing the poor absorption of sulfonamide acids, 0.24 Gm. of sodium sulfadiazine per kilogram of body weight [18] was placed

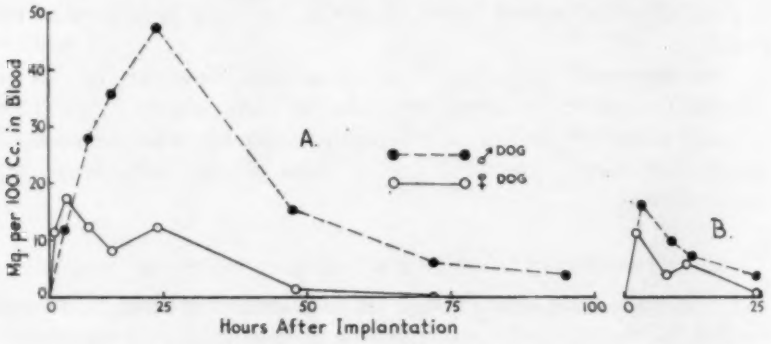

Chart 2.—*A*, the duration of absorption of sodium sulfadiazine powder (0.25 Gm. per kilogram of body weight) implanted in the rectus muscle. *B*, the duration of absorption of sodium sulfadiazine powder (0.1 Gm. per kilogram of body weight) placed in the peritoneal cavity.

into the rectus muscle and sheath of 2 dogs (3 and 5 Gm. respectively, equivalent to 17 Gm. in a man weighing 70 Kg.). The powder when placed into the wound formed a soft paste with the tissue fluids. It was necessary on account of the large volume of powder to compress it into the wound. This produced a localized swelling which existed beneath the skin for several days but which subsided, and the incision healed cleanly. There was no erythema or oozing from the wound to

18. The relatively low chronic toxicity of this drug is exemplified by observations that repeated intraperitoneal injection of 0.3 Gm. per kilogram of body weight in rats proved harmless (Lehr, D., and Antopol, W.: Toxicity of Sulfadiazine and Acetylsulfadiazine in Albino Rats with Special Reference to Renal Lesions and Their Significance, Urol. & Cutan. Rev. **45**:545 [Sept.] 1941).

indicate irritation of the tissues or caustic action by the drug.[19] The concentration of sulfadiazine in the blood and the urine [20] was measured at intervals to ascertain the rates of absorption and excretion. The results as shown in chart 2 *A* indicate that absorption was rapid, resulting in good blood levels within two hours. Although the level declined after thirty hours, levels of several milligrams per hundred cubic centimeters persisted for fifty to a hundred hours. The high blood level in the male dog appears to be peculiar to this animal since subsequent oral administration of sulfadiazine in this dosage (0.25 Gm. per kilogram of body weight) to these same dogs resulted in blood levels around 38 mg. per hundred cubic centimeters in the thin long-boned male dog and around 13 mg. per hundred cubic centimeters in the fat short-boned female dog.[8]

Laparotomy was done on both dogs one week later, and 0.1 Gm. of sodium sulfadiazine per kilogram of body weight (1.2 and 1.7 Gm., equivalent to 7 Gm. in a man weighing 70 Kg.) was poured into the peritoneal cavity. The dogs recovered normally from the operation and remained well. The wounds healed without delay. Determinations of the level of drug in the blood and the urine showed (chart 2 *B*) that absorption was rapid but not more rapid than after intramuscular implantation and that good levels persisted for over twenty hours. Furthermore, the subsequent intraperitoneal implantation of a water-dispersible ointment containing 20 per cent sodium sulfadiazine (0.25 Gm. per kilogram of body weight) gave even more prolonged absorption. The blood level of sulfadiazine, for example, was 11 mg. per hundred cubic centimeters at five hours but was still 3 mg. per hundred cubic centimeters at sixty hours. Significant amounts of drug were excreted in the urine one or two days longer. In these two groups of experiments in dogs as well as in other experiments,[8] only 60 per cent of the drug implanted in the wound could be recovered in the urine. No explanation for this large deficit is yet available.

It is noteworthy that in these experiments the blood levels were similar to those found by Jorgenson [11] after the subcutaneous administration of sodium sulfadiazine in this dosage to infants. This suggests almost identical rates of absorption and excretion of sodium sulfadiazine whether administered subcutaneously, intramuscularly or intraperitoneally.

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19. When sodium sulfathiazole is used, a brownish discoloration of the dog's tissues occurs promptly. This does not occur with sodium sulfadiazine since this sodium salt is readily buffered within the physiologic p_H range.

20. All specimens of urine were examined when voided for drug crystals, p_H and drug concentration. No crystals were found; all specimens of urine were alkaline, their p_H being 8.0 or higher.

COMMENT

These experiments in some measure establish the rationale of local chemotherapy by throwing light on the transport of sulfadiazine when a soluble nonirritating sulfonamide compound is applied locally. It is apparent that oral administration of sulfadiazine or the local use of sodium sulfadiazine in the rectus muscle, in the peritoneal cavity and by clysis under the skin all give similar blood levels. In other words, a given quantity of drug suitably administered by any of these routes is distributed similarly throughout the body. Presumably, then, the major advantages of this type of local therapy are as follows: In the involved local area a high concentration of drug is obtained immediately. In this area the concentration of drug is sustained over a period of twenty-four to forty-eight or more hours while the implanted drug is being transferred continuously but *completely* from the limited local area into the general circulation. As a result, the maximum blood level is attained relatively gradually and subsequently declines slowly. This is in sharp contrast to intravenous injection, which gives the undesirably high maximum blood level almost at once, followed by a rapid decline within two or three hours. Since the implanted drug is removed completely when a soluble derivative is used, foreign body reaction at the local site does not occur.

From these physicochemical measurements and from the preliminary animal experiments certain practical suggestions may be advanced. In the first place, the drawbacks encountered in the local use of sulfathiazole and sulfadiazine which result from their poor solubility may be circumvented by using their soluble sodium salts. The animal experiments prove them (particularly sulfadiazine) to be innocuous and nonirritating to tissues in relatively large doses, but the results of clinical studies now in progress [20a] must be evaluated before it is possible to decide finally on the usefulness of these salts in surgical procedures.

Another practical point is the observation that sulfathiazole and sulfadiazine are extensively ionized at the p_H of the blood and that when they are ionized their solubility is vastly increased over their solubility in water or any of the more common solvents, e. g. oils. This suggests that fluid or semifluid preparations, including ointments, should be prepared from the sodium salts in aqueous and not oily bases if high local drug concentrations are desired. For example, in preliminary clinical trials, 5 per cent sodium sulfadiazine in a glycerite of starch

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20a. Since this paper was submitted, sodium sulfadiazine powder has been tried clinically. After repeated direct application no local irritation has been observed.

21. Mayo, C. W., and Miller, J. M.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**:609 (Sept. 25) 1940. Herrell, W. E., and Brown, A. E.: Local Use of Sulfonamide Compounds in the Treatment of Infected Wounds, ibid. **15**:617 (Sept. 25) 1940.

base has shown no inhibition of healing while providing good absorption of the drug. Likewise, for irrigation [21] far more concentrated solutions may be obtained if the drugs are dissolved in suitable buffers instead of distilled water or if the sodium salts dissolved in water are used.

So far as renal excretion is concerned, the acetyl derivatives like the free drugs form soluble sodium salts. Accordingly it seems that safe renal excretion would be insured by favoring sulfonamide salt formation by keeping the urine alkaline. Complete data on this problem will be published elsewhere.[8]

SUMMARY

The far greater antibacterial potency of sulfathiazole and sulfadiazine has been amply demonstrated, but their use locally in surgical procedures has been hampered by side effects resulting from their relative insolubility.

Measurements of the acidity of the drugs (dissociation constants) show that sulfathiazole and sulfadiazine are about as acidic as carbonic acid and that in biologic fluids (p_H 7.5) they exist chiefly in the ionized form. This accounts for the fact that their concentrations in biologic fluids may be many times greater than their solubility in water.

Preliminary trials were made of the local effects of the sodium salts on tissues together with the rate and the extent of absorption of sodium sulfadiazine after intramuscular and intraperitoneal implantation in dogs. The results showed that sodium sulfadiazine in high concentration caused negligible irritation to tissues. Following either intramuscular or intraperitoneal implantation, sodium sulfadiazine is continuously transferred from the site of implantation to the general circulation over periods of twenty-four to forty-eight or more hours. Sodium sulfathiazole, on the other hand, gave evidence of some tissue irritation.

The local application of the sodium salts of sulfathiazole and especially of sulfadiazine warrants clinical trial. This is now in progress.

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TREATMENT OF LARGE GASTRIC ULCERS

RÉSUMÉ OF A TEN YEAR STUDY

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CHICAGO

The correct treatment of large gastric ulcers is not generally agreed on. The question "Is every large gastric ulcer to be operated on?" has aroused much controversy in the past, and it is still disputed.

In this paper evidence is presented to show that every large gastric ulcer is a condition for operation. This conclusion is not based on the belief that every large gastric ulcer is or may turn into a carcinoma, although that is an important factor. The fact that only a small percentage of large gastric ulcers are malignant or may become malignant should not deter from surgical intervention. Neither the patient who has such a lesion nor the clinician who treats him can be at ease if only 5 per cent or less of such lesions are known to turn malignant.

The difficulty of accurately diagnosing whether a large gastric ulcer is benign or malignant has been stressed by numerous investigators and by me in recent publications.[1] It has been often stated that in spite of improvement in roentgen technic, the advent of gastroscopy and improvement in medical management there is still no definite criterion for an accurate diagnosis of large gastric ulcer. Studies in other clinics and at the Cook County Hospital definitely convince one that there are no reliable data obtainable from the history, the physical examination, the laboratory test, the roentgen and gastroscopic examinations or the clinical response to medical treatment which will assure one that a lesion is benign or malignant.

A comparatively high percentage of large gastric ulcers that prove to be benign have a history of only several months' duration, while, con-

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From the Cook County Hospital and the Department of Internal Medicine, the University of Illinois College of Medicine.

1. (*a*) Holman, C. W., and Sandusky, W. R.: Further Observations on the Diagnosis and Treatment of Gastric Lesions, Ann. Surg. **112**:339-343 (Sept.) 1940. (*b*) Allen, A. W., and Welch, C. E.: Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer, ibid. **114**:498-506 (Oct.) 1941. (*c*) Freedman, E., and Goehring, H. D.: Diagnostic Errors in Ulcerative Lesions of the Stomach and Duodenum, Am. J. Roentgenol. **44**:48-58 (July) 1940. (*d*) Easterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, J. A. M. A. **118**:1-5 (Jan. 3) 1942. (*e*) Mass, M., and Steigmann, F.: Carcinoma in Clinically Benign Gastric Ulcer, Illinois M. J. **75**:120-122 (Feb.) 1939.

trariwise, many proved carcinomatous ulcers have a history of gastric disturbances for years (fig. 1). Secondly, some patients with benign gastric ulcers are cachectic, while some with malignant lesions of the stomach present little external appearance of having malignant growths. Thirdly, in contradistinction to what occurs with duodenal ulcer, achlorhydria is not uncommon in patients with gastric ulcer, while a goodly number of patients with a carcinomatous ulcer may have free acid values above 40 degrees (fig. 2). Furthermore, in cases in which there is a large gastric niche the roentgen diagnosis is usually a presumptive one, since nearly all the criteria which differentiate benign from malignant lesions are distorted (fig. 3). Comparison of the roentgen and

Fig. 1.—*A*, roentgenogram of an ulcer with a history of short duration (three months) diagnosed as benign on histologic examination. It was diagnosed as malignant clinically, chemically, roentgenologically, gastroscopically and at operation. *B*, roentgenogram of an ulcer with a twelve year history simulating peptic ulcer. It was diagnosed as malignant on histologic examination. It was diagnosed as benign clinically, chemically and gastroscopically and improved when the patient was subjected to a medical regimen.

histologic reports on such lesions proves the roentgenologist correct in much less than 90 per cent of the cases. Roentgen examination is not the only means which fares badly in the diagnosis of large gastric ulcers; gastroscopy does little better. I have seen instances of a malignant ulcer being called benign and vice versa (fig. 4). Lastly, benign ulcers will often respond poorly to medical treatment, while malignant ulcers may

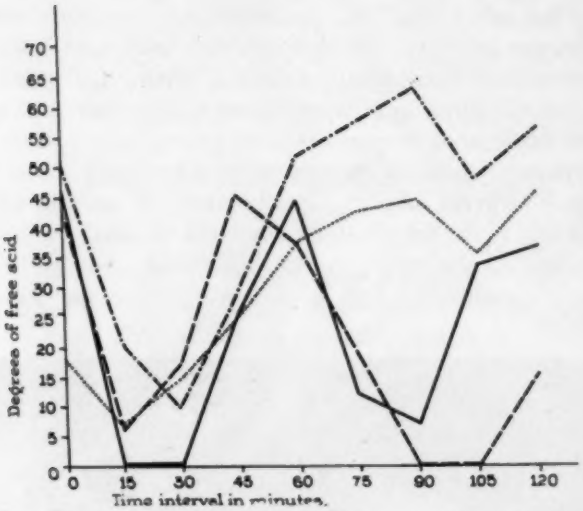

Fig. 2.—Graph showing several acidity curves for a patient with a large ulcerating gastric carcinoma in the pars angularis. The dotted line represents the control curve; the broken line represents the curve for karaya; the solid line, the curve for colloidal suspension of aluminum hydroxide, and the dot and dash line, the curve for acid B, a preparation of dilute nitric acid, bismuth subcarbonate and water.

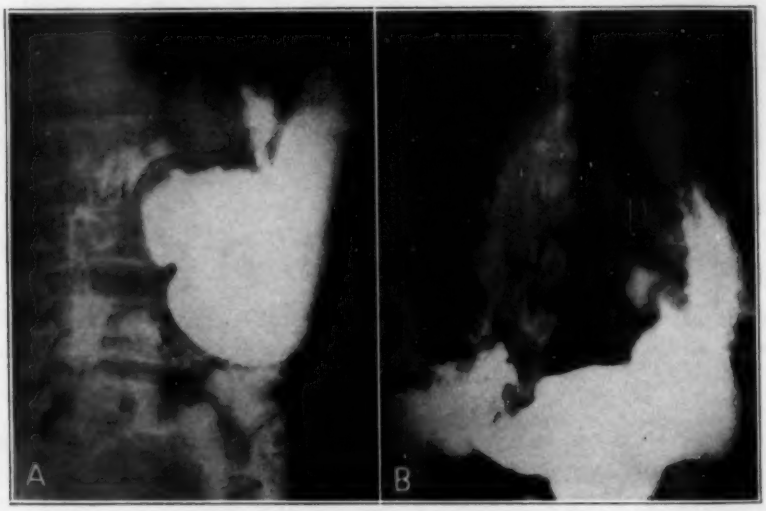

Fig. 3.—*A*, roentgenogram of an ulcer with a short history diagnosed histologically as benign but clinically and roentgenologically as malignant. *B*, roentgenogram of an ulcer with a short history diagnosed histologically as benign and roentgenologically and gastroscopically as malignant.

show a remarkable response to medical treatment and thus give both patient and doctor a false sense of security [1d] (fig. 5).

The surgeon, looking at the exposed lesion, is in many instances unable to tell whether an ulcer is benign or malignant. The pathologist will often fail to tell from the gross appearance of an ulcer whether it is benign or malignant. Only by careful histologic examination of various parts (floor, walls and margins) of an ulcer can one accurately decide on the character of the lesion (fig. 6). The histologic examination of various parts is stressed because frequently one part of the lesion may have a benign appearance while the other parts show signs of malignancy. From these remarks, it is obvious that for a correct

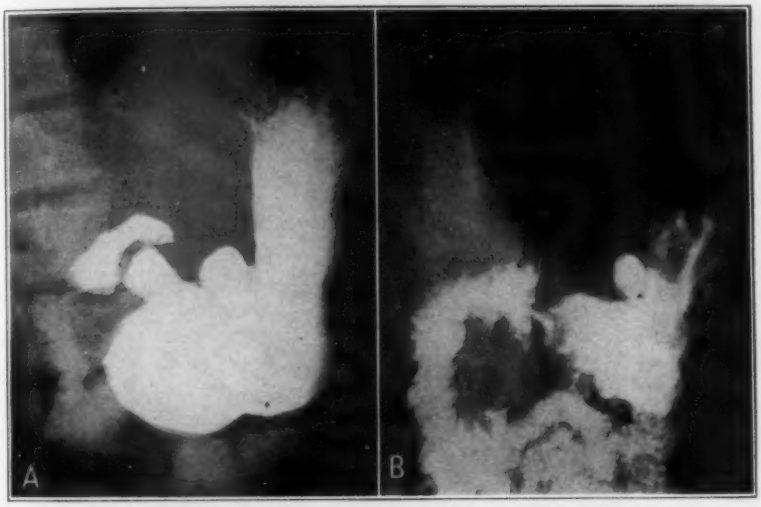

Fig. 4.—*A*, roentgenogram of an ulcer called malignant after histologic examination but benign after gastroscopic examination. *B*, roentgenogram of an ulcer called benign after histologic examination but malignant after gastroscopic examination.

diagnosis of large gastric ulcer histologic examination is imperative, and this entails resection.

Assuming that a large gastric ulcer is benign, one still must ask oneself "Should it be treated medically?" From observations during the past ten years of a large number of patients with large ulcers, it is my opinion that in the majority of cases not much is gained by medical management and that frequently the patient is better off if his lesion is resected as soon as diagnosed, because usually after years of medical management he is finally subjected to surgical intervention.

Owing to ignorance of the causation of peptic ulcer, both gastric and duodenal ulcers are called and treated as peptic ulcers. In reality,

however, the two are different. They differ as to age groups, gastric acidity, complications and treatment. However, there may be as much difference between a large and a small gastric ulcer as between a gastric and a duodenal ulcer. Therefore, it should be emphasized that this paper deals particularly with large gastric ulcers. A large gastric ulcer differs from a small one in the history, the physical examination, the laboratory findings, the roentgen and gastroscopic observations and the response to medical treatment.

With these things in mind, routine surgical intervention is not advocated for all gastric ulcers but for the large ones only. When any ulcer responds poorly to medical treatment, it is presumptive evi-

Fig. 5.—Roentgenogram of an ulcer niche diagnosed as malignant histologically and decreasing to less than one fourth its original size on medical management.

dence that it is malignant. It is certainly not a benign condition which keeps the patient in a chronically ill state, which makes him a chronic invalid and which ultimately sends him to operation for relief of the symptoms. These statements are based on the observation of the life cycle of large gastric lesions. To repeat, even if it is assumed such a lesion is benign, long resistance to treatment, with the probability of complications, indicates operation rather than procrastination with medical management and operation only as a last resort.

It is not within the scope of this paper to give in detail the various complications which may arise from large gastric ulcers, complications

which make them malignant in spite of being histologically benign. I shall mention some of the complications, however, to illustrate the basis for my views.

NONHEALING

It is known that most large gastric ulcers heal poorly under medical management, in spite of the fact that some have apparently healed. I have seen a number of such apparently healed ulcers. Nevertheless, the percentage of relapses is so large that the treatment cannot be considered ideal. It is discouraging to both the doctor and the patient when

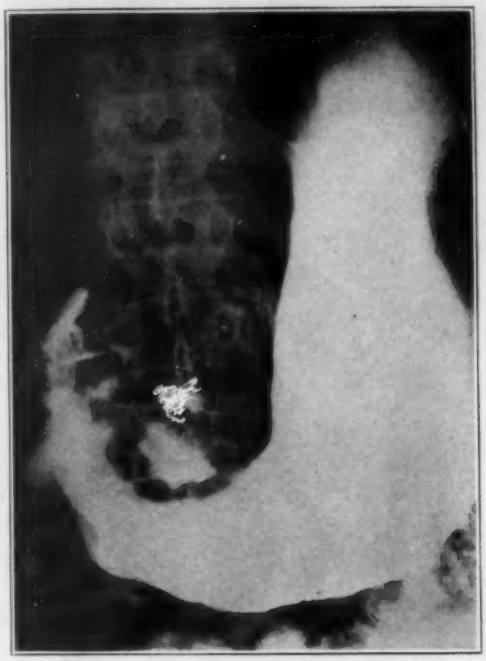

Fig. 6.—Roentgenogram of a large ulcer showing malignant changes on its margin.

a lesion that remains small for months or disappears entirely suddenly develops into a large ulcer.[2] In many instances, medical regimen and even palliative gastroenterostomy do not prevent the ulcer from getting larger and penetrating into the neighboring viscera (fig. 7). Jordan[3]

2. Palmer, W. L.; Schindler, R., and Templeton, F. C.: The Development and Healing of Gastric Ulcer: A Clinical Gastroscopic and Roentgenologic Study, Am. J. Digest. Dis. **5**:501-522 (Oct.) 1938.

3. Jordan, S. M.: The Problems of Peptic Ulcer, S. Clin. North America **21**:665-677 (June) 1941.

expressed the opinion that such a nonhealing lesion indicates operation. It keeps the patient in a chronic state of invalidism until resection relieves him.

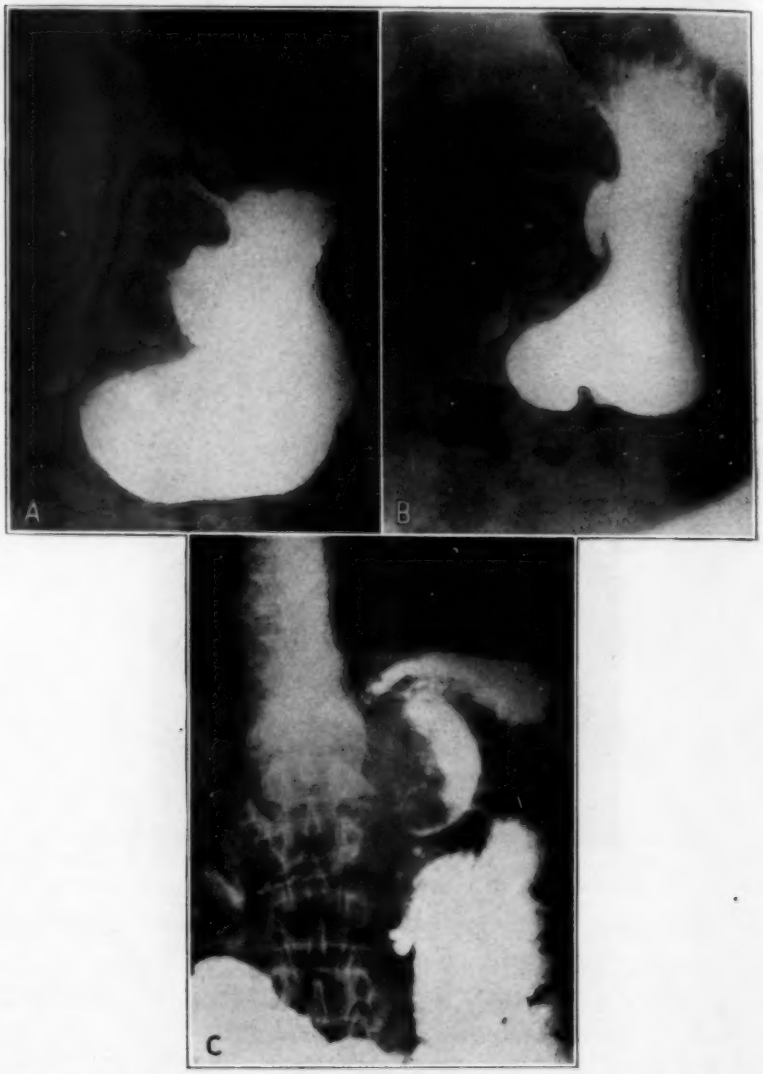

Fig. 7.—Roentgenograms (*A*) of a large benign ulcer which perforated, (*B*) of the same ulcer three months after medical treatment and (*C*) of the same ulcer five years later. In the interim between *B* and *C* the patient underwent gastroenterostomy.

BLEEDING

Hemorrhage from a gastric ulcer is a serious omen at any time. The seriousness, however, is much graver when bleeding occurs from a

large gastric ulcer. The mortality rate associated with bleeding ulcers, both gastric and duodenal, varies in different clinics from 3 to 33 per cent.[4] In this hospital it is around 8 per cent on the average with all types of treatment. However, the mortality from large bleeding gastric ulcers is close to 50 per cent. The reason for this is, of course, obvious, in that the bleeding occurs in an elderly person who has sclerotic vessels which cannot be expected to contract spontaneously. Furthermore, these vessels are usually embedded in cicatricial tissue, which likewise prevents spontaneous contraction of the vessel (fig. 8). Patients with

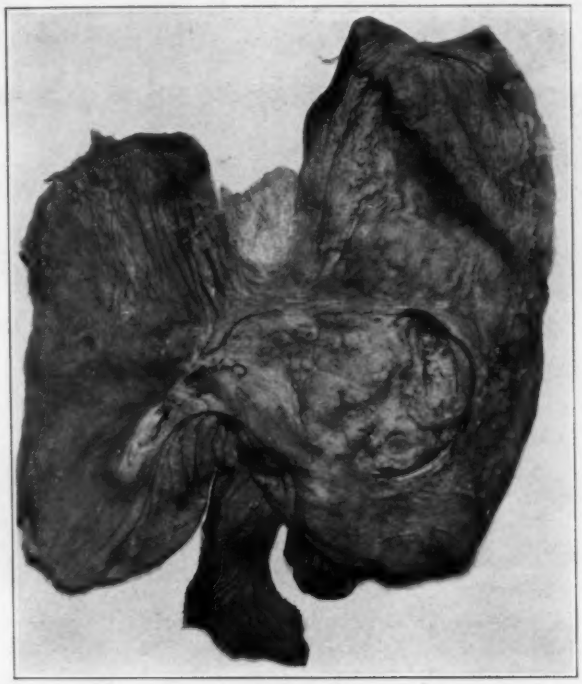

Fig. 8.—Photograph of a large benign ulcer showing gaping blood vessels which led to the patient's death from massive hemorrhage.

such a condition, therefore, present immediate operative emergencies when bleeding occurs. It is clear, moreover, that an elective operation on a large gastric ulcer with careful preoperative preparation is preferred to an emergency operation when bleeding occurs.

4. Allen, A. W.: Acute Massive Hemorrhage from the Upper Gastrointestinal Tract with Special Reference to Peptic Ulcer, Surgery **2**:713-731 (Nov.) 1937. Allen, A. W., and Benedict, E. B.: Acute Massive Hemorrhage from Duodenal Ulcer, Ann. Surg. **98**:736-749 (Oct.) 1933. Blackford, J. M., and Cole, W. S.: Massive Hemorrhage from Peptic Ulcer, Am. J. Digest. Dis. **6**:637-641 (Nov.) 1939. Blackford, J. M., and Williams, R. H.: Fatal Hemorrhage from Peptic Ulcer, J. A. M. A. **115**:1774-1776 (Nov. 23) 1940.

PERFORATION AND PENETRATION

Perforation into the abdominal cavity and penetration into an adjacent organ occur frequently from a large gastric ulcer. Perforation of a large gastric ulcer, while not more frequent than that of any other ulcer, is more serious because the large hole permits more widespread infection. Penetration, however, is a much more common occurrence and actually represents a perforation of the ulcer into the neighboring viscera—the pancreas, the liver and the small peritoneal cavity. At times, spontaneous perforation into the duodenum, the jejunum or the colon occurs.[5] Such penetration leads to formation of adhesions and inflammatory granuloma between the stomach and the particular organs,

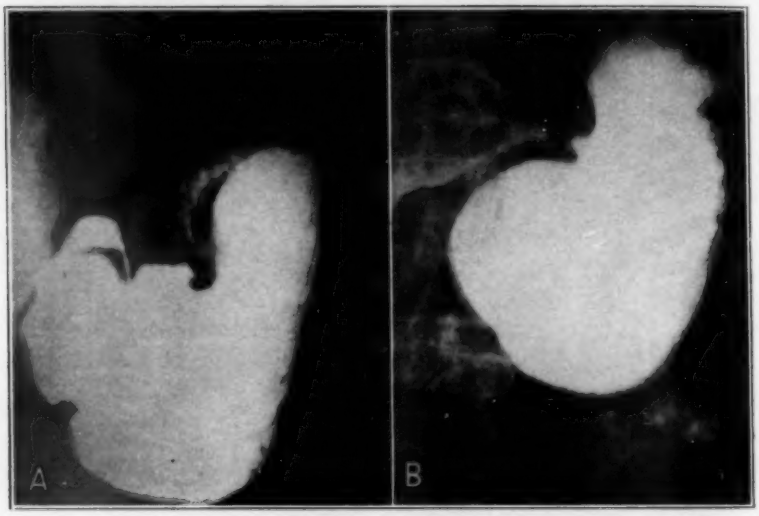

Fig. 9.—*A*, roentgenogram of a large benign ulcer causing tobacco pouch stomach. Note the narrow pylorus close to the base of the gastric ulcer. *B*, roentgenogram of a large benign ulcer causing tobacco pouch stomach.

which in turn produce anatomic deformities that interfere with the motor functions of the stomach and are frequently responsible for many of the so-called intractable ulcer symptoms. Removal of the large gastric ulcer at an early stage would prevent some of these complications.

5. Steigmann, F., and Bach, A. C.: Peptic Ulcer and Gastroduodenal Fistulae, Am. J. Surg. **52**:355-359 (May) 1941. Henke, F., and Lubarsch, O.: Verdauungsslauch, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1. Casellas, R. R.: An Unusual Pathologic Condition of the Stomach with Abnormal Opening into the Jejunum, J. A. M. A. **87**:1393 (Oct. 23) 1926. Monroe, R. T.: Fistula as a Complication of Peptic Ulcer, Am. J. M. Sc. **174**:599-609 (Nov.) 1927.

TOBACCO POUCH STOMACH

The so-called tobacco pouch stomach may produce symptoms and signs resembling those of penetration. The tobacco pouch stomach is one produced by shrinking of the scar tissue of a healed large gastric ulcer with ensuing traction on the duodenal cap leading to shortening and rolling in like a snail[6] of the lesser gastric curvature (fig. 9). This deformity takes years to develop, during which time the patient has various symptoms, and finally it produces symptoms of obstruction which invariably require operation for their relief.

Fig. 10.—Persistent cicatricial hourglass deformity following a large gastric ulcer.

HOURGLASS STOMACH

Severe hourglass deformity following a large gastric ulcer (fig. 10) is the least common complication; I found it in about 4 per cent of the cases in my series. Since it requires surgical intervention and this

6. Ludin, M.: Beiträge zur Magenröntgenologie, Arch. f. Verdauungskr. **32**: 299-312, 1924. Melchart, F.: Zur Frage der Fistula gastroduodenalis im Röntgenbilde, Fortschr. a. d. Geb. d. Röntgenstrahlen **44**:335-342, 1931. Low-Beer, A.: Fistula gastroduodenalis im Röntgenbilde, ibid. **43**:435-441, 1931.

usually on a debilitated patient with symptoms of chronic obstruction, it presents additional proof against the prolonged medical treatment of large gastric ulcers.

CARCINOMATOUS DEGENERATION

The possibility that a gastric ulcer may become malignant has been controverted for many years. Without alining myself with those who believe in such a possibility [7] or with those who stanchly deny it,[8] I may say that I have encountered 3 cases in which a gastric ulcer apparently became carcinomatous. One of the ulcers presented both benign and carcinomatous characteristics in the histologic section. In spite of the fact that my percentage of malignant transformation of gastric ulcers is low, it must be emphasized that this low percentage cannot be used as support of the nonintervention idea for the treatment of large gastric ulcers, since no one can tell definitely or with assurance where this 1 or 2 per cent incidence will fall.

Without presuming to tell surgeons what to do, I may state that in my series of cases high gastrectomy with few exceptions was the procedure of choice in the surgical treatment of large gastric ulcers. Only a few patients had less radical procedure, mainly because anatomic changes and infectious granuloma and cicatricial contraction of these large gastric ulcers prevented or made it unwise surgically to remove two thirds or four fifths of the stomach. All patients had careful preoperative preparation for four to six days, with attention paid especially to their state of hydration, vitamin, mineral and acid-base balance and blood picture. Blood transfusions were given in most instances before and after operation as required. Postoperatively a modified regimen suggested by McNealy [9] was followed. In recent years spinal anesthesia has been the one of choice in these operations. Last but not least, most of the operations were done by men particularly trained and apt in gastric procedures.

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7. Scott, W. J. M., and Mider, G. B.: Malignancy in the Chronic Gastric Ulcer, Am. J. Surg. **40**:47-50 (April) 1938. Bloomfield, A. L.: The Diagnosis of Early Cancerous Changes in Peptic Ulcer, J. A. M. A. **104**:1197-1201 (April 6) 1935. Wilensky, A. O., and Thalheimer, W.: Etiological Relationship of Benign Ulcer to Carcinoma of the Stomach, Ann. Surg. **67**:215-225 (Feb.) 1918.

8. Palmer, W. L.: Benign and Malignant Gastric Ulcers: Their Relation and Clinical Differentiation, Ann. Int. Med. **13**:317-338 (Aug.) 1939. Ewing, J.: Relation of Gastric Ulcer to Cancer, Ann. Surg. **67**:715-724 (June) 1918; Beginnings of Gastric Cancer, Am. J. Surg. **31**:204-205 (Feb.) 1936. Klein, S. H.: Origin of Carcinoma in Chronic Gastric Ulcer, Arch. Surg. **37**:155-174 (July) 1938.

9. McNealy, R. W.: Preoperative and Post-Operative Management of Gall Bladder Disease, J. Kansas M. Soc. **41**:497-502 (Dec.) 1940.

SUMMARY AND CONCLUSIONS

Studies and observations of over 200 patients with large gastric ulcers during a period of ten years lead me to believe that surgical intervention is the treatment of choice, in spite of the fact that many may do well on a medical regimen. This belief is based on the following facts: 1. In most cases of large gastric lesions, a definite diagnosis between benign and malignant cannot be made. 2. Even if benign large ulcers often produce chronic invalidism, they heal poorly, bleed dangerously and even in healing may lead to various complications which ultimately require operation as an emergency measure on debilitated ill patients. 3. Considering the uncertainty of diagnosing such ulcers correctly, their poor and uncertain healing and frequent remissions, their serious complications, even if benign, and their possible although rare malignant degeneration, it seems logical to recommend operation at an early stage.

55 East Washington Street.

RELATION OF SERUM PROTEIN TO WELL HEALED AND TO DISRUPTED WOUNDS

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AND
LOUIS P. KASMAN, M.D.
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In a previous paper [1] we reported observations on the relation of serum protein concentration to wound healing in human beings. The study consisted of details regarding the total protein, albumin and globulin, the albumin-globulin ratio and the calculated protein oncotic pressure of the serum of patients in the postoperative state whose wounds had been carefully observed. These patients fell into three groups, namely, those with clean wounds (hernial and laparotomy), those with deeply infected wounds (below the deep fascia) and those with disrupted wounds. It was concluded that in general patients who had deep infection or disruption of their wounds showed lower values for total protein and for oncotic pressure in their serum. This was due mainly to a diminution in the albumin fraction.

In this paper we shall present additional data regarding the relation of serum protein concentration to clean wounds and disrupted wounds. We shall also present data on total proteins in 1,358 consecutive admissions to our surgical service.

The relation of serum protein concentration to wound healing was studied in 80 patients. Forty had clean well healed wounds, and 40 had disruptions. In 17 of the patients with clean wounds (herniorrhaphies) the determinations were done from one to ten days after operation (average, four days). In the other 23 (clean laparotomy wounds) the determinations were done from one to twenty-two days postoperatively (average, eight days). In 1 case of disruption the determinations were made four days before rupture, and in the other 39 cases of disruption the determinations were made on the day of rupture or the following day.

The values for total serum protein were determined by aeration and titration after micro-Kjeldahl digestion.[1a] The values for albumin were determined after precipitation of globulin with sodium sulfate.

From the Crown Heights Hospital.

1. Koster, H., and Shapiro, A.: Serum Proteins and Wound Healing, Arch. Surg. **41**:723 (Sept.) 1940.

1a. Sobel, A. E.; Yuska, H., and Cohen, J.: Convenient Method of Determining Small Amounts of Ammonia and Other Bases by the Use of Boric Acid, J. Biol. Chem. **118**:443, 1937.

All patients were operated on under spinal anesthesia. Their ages ranged from 18 to 77 years. The average age in the group with clean wounds was 36.5 years. The average age in the group with disrupted wounds was 49.7 years. Sixty-eight per cent of the patients in the group with disrupted wounds had operations for lesions of the duodenum or the stomach or for cancer of some part of the gastrointestinal canal.

All laparotomy wounds were sutured in three layers, continuous plain catgut no. 2 being used for the peritoneum, continuous twenty day chromic catgut no. 2 for the fascia and continuous black silk for the skin. In the hernioplasty wounds the internal oblique muscle and the conjoined tendon (Bassini) or the internal oblique muscle, the conjoined tendon and the external oblique aponeurosis (Ferguson-Andrews) were sutured to the inguinal ligament with interrupted twenty day no. 2 chromic catgut. The skin was closed by continuous black silk suture.

The results are summarized in tables 1 and 2.

It can be seen from the tables that the average values for total protein and the albumin fractions were lower in the patients with disrupted wounds than in the patients with normal wounds. In the patients with disrupted wounds the mean value for total protein was 6.19; the standard deviation, 0.62, and the standard error, 0.102. In the patients with normal wounds the mean value was 6.76; the standard deviation, 1.55 and the standard error, 0.245. That the difference between the means of the patients with disrupted and those with well healed wounds is significant can be seen by applying the formulas:

$$\sigma = \sqrt{S.E._{.1}^{2} + S.E._{.2}^{2}} \text{ and } P = \frac{X}{\sigma},$$

in which σ is the standard deviation of the theoretic distribution of the difference between the means; S. E. is the standard error; P is the probability of the difference being accidental, and X is the numerical difference between the observed means. The result of such a calculation yields a probability of 3.16 chances in 100 of the difference between the means of the patients with disrupted and those with well healed wounds occurring accidentally; this difference of course is significant.

The mean value for albumin in the patients with disrupted wounds was 3.26; the standard deviation, 0.45, and the standard error, 0.07. The mean value in the patients with well healed control wounds was 4.21; the standard deviation, 1.38, and the standard error, 0.22. The calculation of significance of the difference between the albumin mean values in the patients with disrupted and those with normal wounds according to the formulas already given yields a probability of less than 1 chance in 10,000 that such difference could occur accidentally. This confirms our previously reported observation [1] that the fall in total proteins found in patients with disrupted wounds is due entirely to the

loss of albumin and suggests strongly that a more accurate picture of protein disturbance can be obtained if besides total protein the albumin fraction is also determined.

In an earlier report we presented data on serum protein concentration in 7 cases of wound disruption; these data are incorporated in this paper. Subsequently, Hartzell and associates [2] reported the serum

TABLE 1.—*Values for Serum Protein, Serum Albumin and Serum Globulin in Forty Patients with Clean Operative Wounds*

Days Between Operation and Determination	Protein (Gm. per 100 Cc. Serum)	Albumin (Gm. per 100 Cc. Serum)	Globulin (Gm. per 100 Cc. Serum)
7	5.46	3.52	1.94
2	5.64	4.56	1.08
2	5.74	4.38	1.36
22	5.75	2.82	2.93
8	5.87	3.64	2.23
2	5.88	3.46	2.42
3	5.96	4.21	1.74
1	5.95	3.84	2.11
12	6.01	3.69	2.32
9	6.05	3.85	2.20
8	6.09	3.84	2.25
1	6.15	4.58	1.57
5	6.17	4.05	2.12
7	6.20	3.90	2.30
14	6.38	4.61	1.77
10	6.53	4.33	2.20
9	6.59	4.74	1.85
5	6.60	3.18	3.42
19	6.69	4.12	2.57
11	6.72	4.19	2.53
6	6.72	4.12	2.60
10	6.74	4.58	2.16
2	6.75	4.42	2.33
9	6.75	3.46	3.29
3	6.85	4.69	2.16
2	6.88	4.65	2.23
7	7.06	3.76	3.30
10	7.13	3.90	3.23
4	7.25	4.89	2.36
1	7.40	4.02	3.38
11	7.51	4.04	3.47
5	7.57	4.77	2.80
10	7.60	3.54	4.06
2	7.68	4.39	3.29
2	7.75	4.76	2.99
1	7.82	5.13	2.69
8	7.88	4.62	3.26
3	7.90	5.24	2.66
1	8.30	5.33	2.97
2	8.40	5.53	2.87
Mean value	6.76	4.21	
Standard deviation	1.55	1.38	
Standard error	0.245	0.22	

protein concentration in 20 cases of wound disruption to be uniformly below normal values. Using their data and calculating the significance of the difference between their mean values and the mean values found in our cases of well healed wounds as normal, we found further con-

2. Hartzell, J. B.; Winfield, J. M., and Irvin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, J. A. M. A. **116**:669 (Feb. 22) 1941.

firmation that protein disturbance in wound disruption is more evident in the albumin fraction.

The serum protein values in our cases of disruption were not uniformly low. In 11, or 28 per cent, of the 40 cases there were values which ranged from 6.50 to 7.31, averaging 6.94. These are well within normal limits. In 23, or 58 per cent, there were values above 6.0. On the other hand there were 15 cases, or 38 per cent, of the 40 cases of

TABLE 2.—*Values for Serum Protein, Serum Albumin and Serum Globulin in Forty Patients with Disrupted Operative Wounds*

Days from Operation to Disruption	Protein (Gm. per 100 Cc. Serum)	Albumin (Gm. per 100 Cc. Serum)	Globulin (Gm. per 100 Cc. Serum)
10	4.32	2.88	1.44
6	4.50	2.00	2.50
17	5.04	2.80	2.24
8	5.25	3.33	1.92
10	5.51	2.60	2.91
8	5.72	3.39	2.33
6	5.73	3.37	2.36
9	5.74	3.86	1.88
12	5.77	3.24	2.53
9	5.82	2.84	2.98
7	5.86	3.23	2.63
3	5.86	2.90	2.96
8	5.87	2.24	3.63
8	5.91	3.16	2.75
9	5.92	3.64	2.28
7	5.94	3.20	2.74
8	5.96	3.62	2.34
3	6.04	3.04	3.00
13	6.04	3.04	3.00
12	6.05	3.09	2.96
6	6.05	3.09	2.96
9	6.08	3.07	3.01
6	6.12	3.06	3.06
15	6.14	3.09	3.05
8	6.18	3.07	3.11
9	6.25	3.74	2.51
4	6.30	4.22	2.08
13	6.38	3.80	2.58
10	6.38	3.80	2.58
6	6.70	2.98	3.72
7	6.70	2.98	3.72
9	6.71	3.61	3.10
16	6.81	3.72	3.09
5	6.86	3.81	3.05
8	6.86	3.66	3.20
7	6.96	3.81	3.15
5	7.12	3.47	3.65
8	7.16	3.54	3.62
5	7.17	3.60	3.57
8	7.31	3.92	3.39
Mean value	6.19	3.26	
Standard deviation	0.62	0.45	
Standard error	0.102	0.07	

clean abdominal wounds in which total protein values were less than 6.50, ranging as low as 5.46.

Similarly in 7, or 18 per cent, of the 40 cases of disruption there were albumin values of more than 3.75 Gm. per hundred cubic centimeters, whereas in 8, or 20 per cent, of the 40 cases of clean wounds there were values of 3.75 or less.

Among the 20 cases studied by Hartzell and associates [2] there were only 5 cases in which there was a total protein concentration greater

than 6.0, whereas we had 11 cases of disruption in which there were values above 6.5. Because of the small number of cases this difference need not be significant.

There is a great likelihood that the protein values in our well healed cases are low. The table of normal values for serum protein and the albumin fraction representing 9 different groups of observations collected by Muntwyler [3] shows a 7 per cent value for total protein and a 4.6 per cent value for albumin. These values cannot be used for comparison because the complete data are lacking and standard deviations thus cannot be calculated.

The literature regarding serum protein values is not satisfactory. Some time after the study of serum protein relation to disruption had been started, we decided to obtain our own data, and we did determinations on patients in a consecutive series of 1,358 hospital admissions to our surgical service. In these cases total proteins were calculated by the specific gravity method.[4] We found an average value of 6.88 Gm. per hundred cubic centimeters. The range was between 4.9 and 8.2; the standard deviation was 0.173, and the standard error was 0.0047 (see chart).

If these data are used as representative of an average normal for comparison with the values of total protein in our cases of disrupted wounds, the difference is statistically highly significant.

In this series of 1,358 cases of routine serum protein concentration observations there were 4 cases of wound disruption, an incidence of 0.29 per cent. (This is in close agreement with our previously reported findings [5] of 17 disruptions in 7,892 laparotomies, an incidence of 0.22 per cent.) These 4 cases of disruption had serum protein concentrations ranging from 6.3 to 7.3. As can be seen from the distribution curve, there were 87 cases in the series in which the protein concentration ranged from 4.8 to 6.0, and in none of these did disruption occur. This seems to emphasize the previously expressed opinion that the occurrence of normal concentration of serum protein and albumin in some patients whose abdominal wounds have disrupted and of relatively low concentrations in many with clean wounds means that hypoproteinemia by itself is neither a necessary nor a sufficient condition for the development of wound disruption.

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3. Muntwyler, C.: Plasma Proteins, in Piersol, G. M., and Bortz, E. L.: The Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1932, vol. 6, p. 430.

4. Barbour, H. G., and Hamilton, W. F.: Blood Specific Gravity: Its Significance and a New Method for Its Determination, Am. J. Physiol. **69**:654, 1924.

5. Koster, H., and Kasman, L. P.: Wound Disruption, Am. J. Surg. **31**: 537, 1936.

A most striking example is found in a recent case not included in the groups presented in the tables.

REPORT OF A CASE

J. K., a white man 26 years of age, a clerk by occupation, was admitted to the hospital on Dec. 29, 1941. He complained of sudden sharp severe cramplike pains across the middle of the abdomen three years previously; these had gradually subsided in three days. There was no accompanying nausea, vomiting, fever, anorexia, distention or diarrhea. He was well for one year, and then he had another milder attack which subsided in three days. Eight months later there was a third attack and eight months after that a fourth attack. Two years

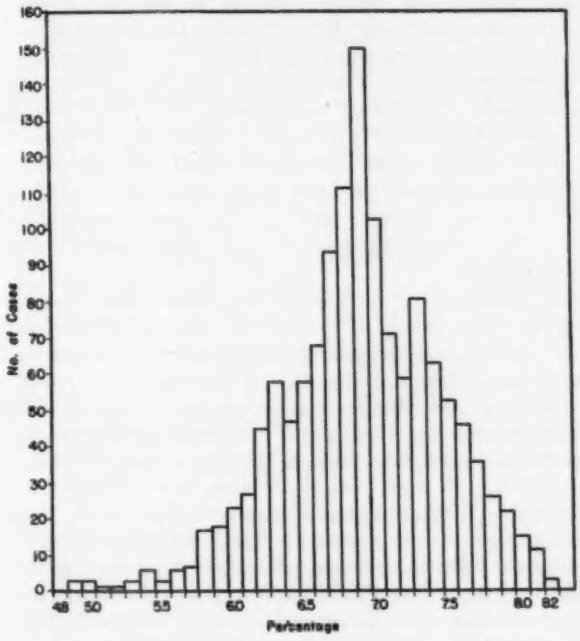

Chart showing frequency distribution curve of total serum protein values in 1,358 patients on whom operation was performed.

before admission his bowel habit gradually changed from two formed stools daily to three or four stools daily of semisolid and sometimes watery consistency. This semidiarrhea would last one to three days, and then the stool would become more solid. These stools were not accompanied by any cramps or pain. During the last year before admission the diarrhea (which became worse) was associated with borborygmus, and the patient himself noticed peristalsis on the abdominal wall. Three months before admission swelling of the legs, the thighs and the scrotum developed, and he had abdominal cramps constantly. For the last few weeks before admission the diarrhea was almost constant, and the stools were foamy, and he had dyspnea on walking. He lost 37 pounds (16.8 Kg.) in the last fifteen months.

The patient related a previous history of asthma at the age of 10 and bronchitis which was relieved after a series of treatments with vaccine. He underwent tonsillectomy fourteen year before admission.

Physical examination revealed pallor of the face and emaciation of the body with edema of both lower extremities, the scrotum and the penis and a large distended abdomen with visible peristalsis. There were numerous coarse and sonorous rales over both lung fields. The heart sounds were of good quality with no murmurs. The abdomen was not tender. There were no palpable masses, but borborygmus was evident. There was a fluid wave in the abdomen, and there was pitting edema of the thighs and the legs. The blood pressure was 102 systolic and 64 diastolic. Roentgen examination showed a normal chest. Electrocardiographic examination revealed no abnormalities. A gastrointestinal roentgenogram showed the entire ileum distended as a result of an obstruction at the ileocecal junction. An enema of barium sulfate also showed the ileocecal obstruction. The hemoglobin was 64 per cent. The red blood cell count was 3,260,000. The white blood cell count was 10,400. The differential count showed 76 per cent polymorphonuclear leukocytes, 21 per cent lymphocytes and 3 per cent mononuclear cells. The urine was normal. The Kahn test gave negative results. The sedimentation time was normal. Blood chloride, calcium and urea nitrogen were all normal. The total protein was 4.6; the albumin, 1.8; the globulin, 2.8. The glucose tolerance test gave normal values. The stool showed no evidence of dysentery, bacillary and amebic. The basal metabolic rate was —20 per cent. The Rehfuss test meal showed normal gastric secretion. There was no blood in the stool.

The absence of significant cardiac or renal involvement suggested that the edema was of nutritional origin as a result of a low grade intestinal obstruction accompanied by defective absorption and assimilation from the small intestine. The obstruction was believed to be due to terminal ileitis. The patient was prepared for operation by a diet high in protein and vitamins, including mineral salts, and blood transfusions. One cubic centimeter of mercupurin given intramuscularly on the day after admission at 1:30 p. m. was followed by an output of 142 oz. (4,199 cc.) of urine within six hours with an intake of only 18 oz. (532 cc.) of water. In the subsequent twelve hours 900 cc. more urine was eliminated, and the edema was practically gone the following morning. Three days after admission he was operated on under spinal anesthesia. There was still some fluid in the peritoneal cavity. Adhesions of the ileum to the cecum were noted, and there was a stenotic lesion at the ileocecal junction with tremendous distention of the ileum, which was larger than twice the size of the colon. The ileum had the characteristic thickening and hoselike rigidity of regional enteritis. A resection of 18 inches (46 cm.) of the terminal ileum, the cecum and the ascending colon to the middle of the transverse colon was done. Postoperatively the patient received one more transfusion. He made an uneventful recovery with primary wound healing. Sixteen days following the day of his operation despite the transfusions the blood protein was 4.4; the albumin was 2, and the globulin was 2.4. Twenty-one days postoperatively the total protein was 5.3; the albumin was 2.3, and the globulin was 2.92. Twenty-seven days postoperatively the total protein was 6.24; the albumin was 2.56, and the globulin was 3.68. There was still an inverted albumin-globulin ratio of 0.7.

The protein concentrations in this case were lower than any in our series of disruptions, low enough to result in nutritional edema, and yet the wound healed without dehiscence.

There is a voluminous literature on the healing of wounds, but information regarding the role of serum protein is meager. There are some facts concerning the effect of diet on wound healing, and from these many inferences have been drawn, some of which at least may be unwarranted. Thus Clark [6] showed that the latent period in wound healing (the time from the injury up to the time of fibroblast proliferation of Carrel [7]) may be shortened almost to the point of elimination by a protein diet. The fact that proteins stimulate cellular proliferation has been shown in other ways.[8] Harvey and Howes,[9] studying wounds in the stomach, found no diminution in the latent period with a high protein diet, but noticed an increased velocity of fibroplasia and its earlier termination once the process was initiated. As a result the maximum strength of the wound was attained earlier than with animals on a standard diet. Howes, Briggs, Shea and Harvey [10] found that the rate of return of tensile strength in adult rats was not affected by complete or partial starvation, although a half adequate diet did result in retardation in young rats. Similarly Morgan [11] showed that regeneration after amputation of legs of salamanders occurred as rapidly during starvation as when they were well fed.

Thompson, Ravdin and Frank [12] reported that the abdominal wounds of 8 of 11 dogs previously fed a restricted diet and subjected to repeated plasmapheresis disrupted or failed to heal. They with Rhoads [13] subsequently failed to obtain disruption in 3 similarly prepared dogs which

6. Clark, A. H.: The Effect of Diet on the Healing of Wounds, Bull. Johns Hopkins Hosp. **30**:117, 1919.

7. Carrel, A.: The Treatment of Wounds, J. A. M. A. **55**:2148 (Dec. 17) 1910.

8. Doberauer, G.; Hoke, E., and Pittrof, E.: Experimentelle Untersuchungen über Wundheilung, Med. Klin. **12**:853, 1916. Herrmannsdorfer, A.: Ueber den Einfluss der Nahrung auf die Pufferkapazität des Blutes und den Heilverlauf und Keimgehalt granulierender Wunden, Deutsche Ztschr. f. Chir. **200**:534, 1927. Reimers, C., and Winkler, H.: Experimentelle Untersuchungen zur Wundheilung und ihre Beeinflussung durch "Azidose" (saure Kost), ibid. **241**:313, 1933.

9. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on Velocity of Growth of Fibroblasts in Healing Wounds, Ann. Surg. **91**:641, 1930.

10. Howes, E. L.; Briggs, H.; Shea, R., and Harvey, S. C.: Effect of Complete and Partial Starvation on Rate of Fibroplasia in Healing Wound, Arch. Surg. **27**:846 (Nov.) 1933.

11. Morgan, T. H.: The Physiology of Regeneration, J. Exper. Zool. **3**: 457, 1906.

12. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **36**:500 (March) 1938.

13. Thompson, W. D.; Ravdin, I. S.; Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, Arch. Surg. **36**:509 (March) 1938.

postoperatively received lyophilized serum intravenously to raise the serum protein content. They suggested that hypoproteinemia was a factor in the mechanism of disruption and that retardation in healing of wounds associated with hypoproteinemia might be averted by restoration of the serum protein to normal levels immediately after operation.

Unfortunately their papers contain no data on the actual concentration of serum protein and its fractions, the percentage of disruptions in the 8 dogs whose wounds were considered to have unsatisfactory healing or the relation of infection to the unsatisfactory healing in those of the 8 dogs without disruption. Then too, while protein starvation and repeated plasmapheresis do produce hypoproteinemia, there is little evidence that it is the only metabolic disturbance in animals treated in this manner. Thus it is difficult to evaluate their results or to apply them to the problem in human beings.

Since there is no direct evidence of the importance of a high serum protein level for satisfactory wound healing, in the light of our findings it seems fair to say that at present the poor nutritional state of which hypoproteinemia is a manifestation may favor wound disruption.

SUMMARY

Data on total protein concentration in 1,358 consecutive admissions to a surgical service are presented. In this series there were 4 cases of wound disruption; in all of these there was a relatively high concentration.

The average serum protein concentration in 40 cases of wound disruption was significantly lower than in 40 cases of control well healed wounds.

The occurrence of relatively high serum protein concentration in cases of wound disruption and low concentration in cases of well healed wounds suggests that hypoproteinemia by itself is neither a necessary nor a sufficient cause for wound disruption.

A poor nutritional state of which hypoproteinemia is a manifestation may favor wound disruption.

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NEW METHODS FOR DETERMINING THE VIABILITY OF BOWEL

PRELIMINARY REPORT WITH CLINICAL CASES

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The establishment of the viability of the bowel in cases of strangulated hernia is of great importance in abdominal surgical procedures at the time of operation since resection of the bowel considerably increases the operative hazard.

In Frankau's [1] series of cases of strangulated hernia immediate resection and anastomosis showed a mortality rate of 42.8 per cent, while in cases in which resection was not done the mortality rate was only 14.7 per cent. In the series of Braun and Wortmann [2] the mortality rate associated with resection was 50.4 per cent, while in their cases of strangulated hernia in which resection was not done the mortality rate was only 14.8 per cent. Since the decision concerning the viability of the intestine must be made within a short time after the abdomen is opened, the surgeon often finds himself in a quandary as to whether or not the intestine is beyond recovery. Stone [3] stated that this is one of the many occasions when the widest experience may prove fallacious and the best judgment faulty. The extremes, as usual, are

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The fluorescein solution used in this study was supplied by C. F. Kirk & Co., New York.

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1. Frankau, C.: Strangulated Hernia: Review of 1,487 Cases, Brit. J. Surg. **19**:176-191 (Oct.) 1931.

2. Braun, W., and Wortmann, W.: Der Darmverschluss und die sonstigen Wegstörungen des Darmes, Berlin, Julius Springer, 1924.

3. Stone, H. B.: Hernia, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 7, chap. 9, pp. 1-66.

easily dealt with. It is the intermediate case in which decision is difficult. But this decision, if erroneous, may lead to death in a great number of cases.

The methods now used in doubtful cases rely mainly on the return of pulsation in the arteries of the bowel segment concerned and on the return of a pink color, especially after warm compresses have been used for some time. This procedure in turn prolongs the operation and may add further hazards, particularly the damage to the serosa produced by the hot pads used in laparotomy. Thus far no method has been devised which shows immediately and objectively whether the circulation in the bowel will be reestablished after strangulation is released.

The following possibilities have presented themselves, namely, the use of fluorescein, the local use of procaine hydrochloride and the inhalation of pure oxygen. This investigation was given impetus by Dr. Herbert C. Chase, who employed oxygen for the recognition of viability of the intestine in dealing with loops presenting doubtful circulatory competence. A subsequent report will deal with the application of oxygen and also with the effects of the various types of anesthesia in relation to the viability of the bowel.

FLUORESCEIN TEST

Recent observations in our laboratories proved that the fluorescent effect of fluorescein,[4] which had been used in the objective determination of circulation time,[5] would also reveal the presence and adequacy of circulation in the intestine. Since then the opportunity for further study of this phenomenon presented itself both in experimental animals and in 6 patients with strangulated hernia.

The fluorescein test is performed as follows: After exposure of the questionable loop of bowel and release of the strangulation, the operating room is slightly darkened, and the color of the intestines is observed under purple light. Fatty parts of the mesentery may show a yellowish tint owing to a certain fluorescence inherent in adipose tissue. Five to 6 cc. of a 5 per cent solution of fluorescein (in dogs 1 cc. only is used) to which sodium bicarbonate is added to make a 5 per cent solution is then rapidly injected intravenously. The rays of an ultraviolet bulb which is covered with a purple glass filter (Wood filter) are directed by an assistant into the questionable loop of bowel. This special filter permits the passage of only a wavelength of 3,500 to 4,000

4. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, M. Clin. North America **26**:943-952 (May) 1942.

5. Lange, K., and Wollheim, E.: The Circulation Time and Its Relation to Other Factors of the Circulation, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **43**: 134-140, 1931.

angstrom units, thus giving a dark purple light effect on the tissue. After the circulation time has elapsed, the fluorescein appears in the vessels of the bowel, producing a characteristic golden green illumination of only those areas sufficiently supplied with blood. Districts which are not viable and accordingly out of circulation remain purple, while other segments inadequately supplied show markedly diminished illumination and often have a patchy character. These effects are so conspicuous that the naked eye easily observes the entrance of blood into the smaller vessels and the further spread into the serosa.

Fluorescein seems to be nontoxic. We have given up to 15 cc. intravenously in clinical cases and have examined nearly 500 patients with the method. We were unable to observe reactions of any kind in this series. Fluorescein is rapidly excreted into the urine, and with a normal renal function it is no longer visible in the plasma after five hours have elapsed.

PROCAINE HYDROCHLORIDE

Recent advances in the knowledge of peripheral vascular diseases suggested the application of our newer knowledge of the effects of procaine hydrochloride on circulatory changes in the bowel. The marked objective changes in the intestine could readily be accounted for by the end results of vasospasm which in itself is reflex in character. Furthermore, the established efficacy of procaine hydrochloride in releasing arterial and venous constrictions by means of inhibiting the autonomic impulses could be applied in the investigation of the circulatory competency of the intestine. These principles were applied in our experimental and clinical cases with excellent results.

EXPERIMENTAL EVIDENCE

In a series of 7 rabbits a strangulation of the intestine was produced by putting a rubber band under an exact predetermined tension around a loop of small bowel about 3 inches (7.6 cm.) long. The pressure exerted at the place of constriction was always far above the systolic pressure. This strangulation was maintained for different periods as shown in the table.

After the rubber band was released, fluorescein was injected intravenously, and the appearance of the strangulated loop in contrast to the normal bowel was observed. Up to a time limit of two hundred and twenty minutes, full fluorescence of the formerly strangulated loop appeared within a few seconds; only beyond this period parts of the bowel failed to show full fluorescence. Small serosal areas maintained a persistent purple hue. After two hundred and fifty-five minutes, however, no return of fluorescence after injection of the solution could be noted; this was evidence that the vascular tree leading to this area was definitely occluded. Hot pads failed to restore the circulation in this particular loop. One fact, however, was conspicuous. Even in those animals in which the duration of strangulation was only two hundred minutes, the gross appearance of the bowel was altered in color

to so great a degree that surgical judgment would have suggested resection in a comparable clinical case. Immediate recovery of the circulation was revealed by the fluorescein test. It was felt that the intensity of the color changes in the production of strangulation was primarily due to venous congestion.

Using a sharp clamp for occluding the vessels of the intestine, irreversible damage to the vessels, indicated by an entirely negative or patchy reaction to the fluorescein test, was produced in 4 rabbits after twenty-five minutes.

In a series of 5 dogs the strangulation of the small bowel by a rubber band of exactly predetermined tension was repeated. These tests, however, were modified by injecting 2 per cent procaine hydrochloride around the main vessels leading to the strangulated district. This method, which had already proved its diagnostic and therapeutic value to two of us (S. T. G. and J. O. H.), showed its merits also in these objective tests. Two loops of small bowel were strangulated under the same pressure, and after a certain period (when the involved portion of intestine appeared dark or was approaching a black color) both strangulations were released. At the same time fluorescein was injected intravenously, and the intestine was exposed to the special light. It could be noticed that in all cases in which procaine hydrochloride had been injected into the mesentery of one of the loops this loop showed an earlier,

Duration of Strangulation and Restoration of Circulation in Experimental Animals

Animals	Duration of Strangulation (Min.)	Restoration of Circulation	
		Complete	Partial
1	60	+	
2	150	+	
1	220	+	
1	220	—	+ (Patchy fluorescence)
2	255	—*	

* No restitution after 300 min.

more homogeneous and more intense fluorescence than the loop not treated in this manner. If in the loop with the untreated vessels only patchy fluorescence could be seen for some time, injection of procaine hydrochloride along the vessels leading to such a segment often produced an immediate return of circulation and peristalsis in the area which had previously been purple.

A more rapid response to procaine hydrochloride was noted when the injection was made at the mesenteric border of the bowel than when the injection was made around the larger vessels. This observation was even more noticeable at the site of the constriction rings. It has not been determined whether procaine hydrochloride exerts an additional effect on the smooth muscle of the intestine aside from the effect on its autonomic nerve supply.

Since in strangulated hernias the serosa sometimes is found torn or scraped off the muscularis, we reproduced this condition by stripping part of the bowel of its serosa. Under normal conditions such denuded areas are less transparent and contain considerably fewer capillaries. This accounts for the markedly diminished intensity of the fluorescence in the absence of serosal tissue. However, if normal circulation prevails in this region of exposed muscularis, a few capillaries always show up with good fluorescence, and if this is not the case, injection of procaine hydrochloride along the vessels supplying the area makes them appear immediately.

CLINICAL EVIDENCE

CASE 1.—W. C. had right inguinal hernioplasty performed for an incarcerated inguinal hernia on Sept. 13, 1941. General anesthesia was used. The hernial sac was dissected free of the scrotum. A strangulated loop of small intestine was found when the sac was opened. The portion of intestine was approximately 10 cm. in length and blackish in color for a distance of 6 cm. The patient was given 100 per cent oxygen by inhalation, and warm laparotomy pads were applied on the bowel. After a lapse of five minutes there was practically no return in circulation. Procaine hydrochloride (5 cc. of 2 per cent solution) was injected into the root of the corresponding segment of the mesentery around the blood vessels. Within one minute the bowel had acquired a pinkish hue, and active peristalsis developed throughout the affected part of the intestine. The bowel was then replaced into the peritoneal cavity, and the wound was repaired in the usual manner. Recovery was uneventful.

CASE 2.—J. K. had left inguinal hernioplasty performed for incarcerated inguinal hernia on March 25, 1942. General anesthesia was used. When the hernial sac was opened, a large amount of hemorrhagic fluid escaped. A loop of strangulated small intestine about 10 cm. in length was released; its walls were purplish, congested and edematous. An intravenous injection of fluorescein was given, and the intestine was inspected under the ultraviolet light. An area about 3 by 4 cm. showed no circulation. Hot packs were applied, and 100 per cent oxygen was given by the closed system. Moderate improvement was noted, but there still remained a segment of the intestine about 2 cm. in length which was devoid of circulation as shown by the fluorescein test. About 10 cc. of 2 per cent solution of procaine hydrochloride was injected into the mesentery corresponding to the involved loop, and within two minutes following this procedure fluorescence was noted throughout the involved region. The intestine was returned to the peritoneal cavity. Repair of the wound was done in the usual manner. Recovery was uneventful.

CASE 3.—J. W. had right inguinal hernioplasty performed for incarcerated inguinal hernia and hydrocele. General anesthesia was used. A large amount of hemorrhagic fluid escaped when the hernial sac was opened. Approximately 45 cm. of the small intestine was found to be strangulated. Oxygen (100 per cent) was administered by mask. The color of the intestine which had been deep purplish became lighter. Peristalsis, however, was not visualized. About 10 cc. of 2 per cent solution of procaine hydrochloride was injected into the corresponding root of the mesentery, and within thirty seconds active peristalsis was visible. The intestine was returned to the peritoneal cavity, and the usual repair was performed. Recovery was uneventful.

CASE 4.—J. Z. had left femoral hernioplasty performed on Jan. 14, 1942, for a strangulated femoral hernia. Local anesthesia was used. When the hernial sac was opened, about 4 inches (10.2 cm.) of gangrenous small intestine was found. The mesenteric vessels of this segment were thrombosed. An intravenous injection of 5 cc. of fluorescein was given. Under the ultraviolet light excellent fluorescence limited by the blackened gangrenous area was noted. The line of demarcation between the fluorescence and the involved portion of the intestine was sharp. Hot packs, oxygen (100 per cent) by inhalation and injection of procaine hydrochloride into the mesentery failed to revive the gangrenous portion of the intestine. Side to side anastamosis was performed following the resection of the nonviable bowel. Repair of the wound was performed in the usual manner. Postoperatively, the abdominal status was satisfactory; however, the patient died on the tenth day as a result of pneumonia.

CASE 5.—M. A. had left femoral hernioplasty performed on April 1, 1942, for an incarcerated femoral hernia. General anesthesia was used. When the sac was opened, about 10 cm. of small intestine was found to be incarcerated. The application of hot packs and the inhalation of oxygen (100 per cent) gave only slight improvement. The fluorescein test revealed the absence of circulation. Within two minutes after the injection of 4 cc. of 2 per cent procaine hydrochloride along the corresponding mesentery, peristalsis became visible, and the color of the bowel returned to normal. At this time fluorescence was definite. The wound was repaired in the usual manner. Recovery was uneventful.

CASE 6.—K. W. had right inguinal hernioplasty performed on Nov. 11, 1941, for an incarcerated recurrent inguinal hernia. Local anesthesia was used. The peritoneum was opened in the floor and was found to consist of incarcerated omentum. The patient was given 2.5 cc. of a 5 per cent solution of fluorescein intravenously; the room was darkened, and the portion of the omentum the viability of which was questioned was exposed under the ultraviolet light. The absence of fluorescence in the involved omental mass indicated the lack of circulation, and a portion 8 by 10 cm. was resected. The repair was performed in the usual manner. An uneventful recovery followed.

COMMENT

The application of the findings revealed in the animal experiments was exactly borne out in 6 patients, as just reported. After the strangulation was released and the intestine was observed under the purple light, 5 to 6 cc. of 5 per cent solution of fluorescein was given intravenously and the special light directed on the portion of intestine the viability of which was doubtful.

Five hernias contained small bowel, and 1 contained omentum. In all cases the clinical course after operation bore out the correctness of the prognosis based on the fluorescein test, the procaine hydrochloride test or both. In 3 cases only could patchy fluorescence be obtained in parts of the strangulated loop. In 2 of these procaine hydrochloride succeeded in releasing the spasm. In 1 case, however, this attempt failed, and resection was performed. In 2 cases, judging from the gross appearance of the bowel, resection seemed inevitable, but the combined fluorescein–procaine hydrochloride test resulted in satisfactory restoration of the circulation thereby obviating resection. The clinical course in these cases was uneventful, corroborating the prognosis. In 1 case a localized serosal defect failed to show fluorescence. However, injection of procaine hydrochloride along the larger vessels caused the appearance of fluorescence in the muscularis within a few seconds, giving evidence of the return of blood supply to this region.

In many of our animal experiments as well as in 3 of our cases it was evident that the contraction ring at the place of incarceration had not disappeared during the period of observation, although this same district showed homogeneous fluorescence from the beginning. The persistence of the contraction ring, therefore, cannot be considered a proof of nonviability of the bowel.

SUMMARY

A method in which fluorescein is used is described whereby direct visual evidence concerning the viability of an injured portion of the intestine can be established immediately.

Procaine hydrochloride injected along the vessels leading to a strangulated loop of intestine is able to release vascular and muscular spasms, thereby restoring the viability of the intestine. It serves not only as a diagnostic agent but also as a therapeutic measure.

The time of strangulation is the most essential factor for the return of circulation in the bowel thus damaged.

The persistence of the contraction ring at the point of strangulation cannot be considered a valuable diagnostic sign of nonviability of the bowel.

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PROGRESS IN ORTHOPEDIC SURGERY FOR 1941

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

(*Continued from Page 690*)

VII. INFECTIONS OF BONES AND JOINTS, EXCLUSIVE OF TUBERCULOSIS

General Considerations.—Owen,[232] discussing acute hematogenous osteomyelitis, reemphasizes that it is a blood-borne pyogenic infection affecting principally the long bones of children and adults. The early diagnosis is made on the basis of sudden onset of fever, pain, localized deep tenderness and limitation of motion. The original infection is from some distant focus. The author stresses the fact that the earliest local signs are heat and increased tenderness on deep pressure with a normal roentgen picture. The infection spreads rapidly along the medullary cavity, starting in the metaphysis distal to the entrance of the nutrient artery. There is a plugging of part or all of the arterial tree with abscess formation, and as the infection spreads along the medullary canal and through the haversian canals it reaches the periosteum, which becomes undermined and stripped up.

The author stresses the fact that the treatment must be an individual one and proportioned to the type and the severity of the condition in each case. He states that routine early radical operation causes a higher mortality rate in cases in which the condition is acute but feels that in cases in which a single bone is involved drainage should be instituted quickly.

In addition to operation, parenteral administration of fluids, transfusions, constant nursing care, sedation if necessary, absolute rest in bed and splinting of the limb in the selected position should be routine.

In the cases in which the condition was acute the mortality rate has been 13 per cent, and in the cases in which the condition was chronic, 1 per cent.

[ED. NOTE: This is a good article on the general consideration of acute hematogenous osteomyelitis. We also feel that conservatism should be the keynote of the care in cases in which the condition is acute.]

In considering subacute osteomyelitis Forni[233] reports in detail a case of subacute cortical diaphysial osteitis in a boy of 18 years. He

232. Owen, W. B.: Hematogenous Osteomyelitis, South. M. J. **34**:544-547 (May) 1941.

233. Forni, G.: Subacute Cortical Diaphyseal Osteitis in the Adult, Rassegna internaz. di clin. e terap. **22**:81-95 (Feb. 15) 1941.

concludes from a review of the literature that the condition is rare in adults and is usually caused by the staphylococcus, being most frequently observed in young men and varying in type according to the degree of virulence of the organism. In the differential diagnosis one has to consider osteogenic tumors in general and Ewing's tumor in particular, the chronic inflammatory disease of bone and melorheostosis. The treatment is chiefly surgical, and autogenous vaccines may be used as an adjunct to operation.

In the case which the author describes, syphilis was suspected, but the tests yielded negative results. An operation was performed, and the patient was discharged one month later. When seen six months later, he seemed well and was about to enter military service. The symptoms, however, recurred as evidenced by swelling in the lower part of the thigh; this was first diagnosed as sarcoma. At the second operation small purulent foci were found in the cortex, surrounded by granulation tissue. The cavity was disinfected with ether and packed with ointment, and the limb was placed in a plaster cast.

Histologic examination showed marked density of bone. Staphylococcus aureus was isolated, and this organism was found responsible in 11 of 20 cases. The course of the disease in the adult is attributed to an attenuated virulence which produces necrosis rather than suppuration. In some cases there has been a gradual involvement and muscular atrophy. The author states that in about 76 per cent of the cases reported in the literature the patients were females between 11 and 31 years of age.

[Ed. Note: Acute or subacute osteomyelitis in adults is certainly not common.]

In reviewing osteomyelitis Cleveland [234] reports 56 cases of patients treated within the last ten years. He found that in 80 per cent of the cases osteomyelitis was caused by staphylococcus and in the majority of the other cases by streptococcus. Osteomyelitis due to streptococcus tended to give primary joint involvement and was usually found in infants.

In 16 of the total number of cases, involvement of the upper femoral metaphysis invariably caused secondary invasion of the hip joint with subsequent disability. In 4 of the 17 cases in which the lower femoral region was involved, the knee joint was affected.

Plaster of paris immobilization will lessen the chance of pathologic fracture. For the whole series there was a mortality rate of 25 per cent. Of the patients surviving only one third presented disability. In 34 cases of acute hematogenous osteomyelitis of this series there was a

234. Cleveland, M.: Osteomyelitis and Pyogenic Infections of Joints, Bull. New York Acad. Med. **17**:205-220 (March) 1941.

mortality rate of 8.8 per cent. Conservative operation combined with supportive measures was used in all cases.

[ED. NOTE: This is a comparatively low percentage of both mortality and disability, particularly since many of these patients must have been treated without the benefit of chemotherapy.]

Beranger [235] describes a nonsuppurative generalized form of staphylococcic osteoperiostitis in an infant. In the child during infancy there developed recurring attacks of pain and swelling in the right leg, usually without fever, and at 14 months the child was in poor general condition. He presented septicemia, and throughout the course of his illness the roentgenograms revealed no abnormalities except marked sclerosis and periostitis. The patient finally died in spite of toxoid therapy and various types of conservative treatment, the condition being diagnosed hematogenous nonsuppurative diffuse osteomyelitis. The author feels that this was probably a case of Ollier's albuminous osteoperiostitis.

Lewis [236] presents 9 cases for differential diagnosis in which the roentgen appearance was misleading. Two of the patients were thought to have tuberculosis when first seen, and 2 others showed a similar roentgen picture but were considered nontuberculous. One of the patients proved to have a giant cell variant, and of 2 patients with os calcis disease and identical roentgen findings, one was proved to have staphylococcic, and the other a tuberculous, infection. [ED. NOTE: This roentgen study indicates the difficulty and the futility of differential diagnosis of bone lesions based on roentgen examination alone.]

Causation and Pathologic Characteristics.—Bertelsmann [237] presents a discussion of osteomyelitis based on a personal bacteriologic study. He believes that infection may occur in infancy and persist throughout life as a latent infection without symptoms, which will under varying conditions produce osteomyelitis. An injury is to be considered only as a releasing factor, producing exacerbation of an already existing disease, but not as the cause of osteomyelitis except under unusual circumstances. The author is of the opinion that the bacteriologic examination of the blood is of great importance for early diagnosis, for early operation and for the differentiation of mild and severe cases. General hygienic measures, including nutrition in the prenatal period, may help to further reduce the incidence of osteomyelitis. He believes

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235. Beranger, R. P.: Prolonged, Nonsuppurative Generalized Form of Staphylococcic Osteoperiostitis in an Infant: Case Report, Dia méd. **13**:222-224 (March 31) 1941.

236. Lewis, R. W.: Cases of Nonspecific Bone Infection with Unusual or Obscure Features, Am. J. Roentgenol. **46**:659-666 (Nov.) 1941.

237. Bertelsmann, R.: Hematogenous Osteomyelitis, Monatschr. f. Unfallh. **47**: 237-247 (Aug.) 1940.

that if the infection develops following an injury to the metaphysial region that Staph. aureus was probably present at this site before the injury.

Goodyear [238] discusses the causation and the pathogenesis of purulent polyarthritis due to Streptococcus viridans. He presents a case of infection occurring in a 7 week old infant in which the elbow, the shoulder and the mandibular joints were involved and believes that the infection was transmitted from the mother before birth. [ED. NOTE: Proved Str. viridans in an infant of 7 weeks is rare, and the author infers that temporary immunity is not always present in early life and that it may be overcome by a massive infection.]

Canavero and Maggi [239] discuss the classic Lexer osteomyelitis experiments demonstrating that a local bone lesion can produce osteomyelitis only if pus-forming organisms are already circulating in the blood. The authors have confirmed the experiments of Lexer. Twenty-five rabbits were given injections of pathogenic anaerobes. Purulent or necrotic processes in the bone marrow or the diaphyses of the long bones were not produced. After repeated injuries to the surface of the bone, however, a similar injection produced the characteristic osteomyelitic foci and a marked local reaction.

Richardson and Ranking [240] report a metastatic bone infection with terminal meningitis caused by Bacillus coli. In the case reported the patient was a man of 57 who was vaguely ill and was found to have pus cells and B. coli in the urine. Swelling and induration appeared on the right fibula with nodules that were tender and painful, and from these B. coli pus was aspirated. The early roentgen examination revealed no abnormalities, but later examination showed extensive involvement of the right tibia and fibula. There was no response to chemotherapy, and the patient died, presenting at autopsy cultures from the subarachnoid space which yielded a growth of B. coli.

Chandler and Breaks [241] report a case of osteomyelitis of the femoral head and neck caused by Bacterium necrophorum. This occurred in a child of 12 years with a draining left ear, pain in the right hip and evidence of generalized sepsis. Pus smears and cultures showed many

238. Goodyear, E. S.: Purulent Polyarthritis Due to Streptococcus Viridans: Its Occurrence in Infant of Seven Weeks, Am. J. Dis. Child. **61**:342-343 (Feb.) 1941.

239. Canavero, M., and Maggi, E.: Experimental Osteomyelitis Due to Pathogenic Anaerobic Bacteria, Policlinico (sez. chir.) **48**:1-22 (Jan.) 1941.

240. Richardson, P. L., and Ranking, J. M.: Metastatic Bone Infection with Terminal Meningitis Due to B. Coli, Brit. M. J. **2**:743 (Nov. 30) 1940.

241. Chandler, F. A., and Breaks, V. M.: Osteomyelitis of the Femoral Neck and Head Caused by Bacterium Necrophorum, J. A. M. A. **116**:2390-2392 (May 24) 1941.

gram-negative bacilli with bipolar and granular forms. The organisms were anaerobic and identical with Bact. necrophorum. The ability of this organism to invade tissue and become localized is demonstrated, and the authors point out that the focus in children is often otitis media with mastoiditis. The authors feel that infection by this organism is more common than is generally supposed. [ED. NOTE: The chronic course of the disease is similar to that of ordinary staphylococcic osteomyelitis.]

Kini and Kesavaswamy [242] discuss the role of smallpox in the production of deformities caused by bone and joint infections, reporting 21 cases of osteomyelitis associated with smallpox and 4 associated with vaccination. In all of the cases in which there were joint manifestations the end result was ankylosis; in 1 of these cases resection of the elbow later gave an excellent result. [ED. NOTE: This interesting report should be recorded, but we have never encountered destructive bone or joint lesions associated with smallpox or directly attributable to vaccination.]

Tunick and Stone [243] report a case of osteomyelitis in which nine bones in the body were involved following prostatic abscess and bilateral bronchopneumonia. In this case in the chronic stage there was no spontaneous sequestration or development of draining sinuses over a three year period, and a gram-negative Friedländer bacillus was found. Some authors consider this bacillus as only a secondary invader, but Tunick and Stone state that the Friedländer bacillus is found in 10 per cent of the cases of croupous pneumonia and in 23 per cent of the cases of bronchopneumonia.

Jensen [244] presents a case of sclerosing osteomyelitis of the lower end of the femur without suppuration in a 20 year old woman. At operation staphylococcus was found, and the author believes this was a case of chronic sclerosing osteomyelitis of Garré but points out the difficulty of sometimes confusing this condition with syphilis or Ewing's tumor.

Experimental.—Scheman, Janota and Lewin [245] discuss the experimental production of osteomyelitis and offer a preliminary report on a method of producing lesions simulating human osteomyelitis. In these

242. Kini, M. G., and Kesavaswamy, P.: Role of Smallpox in Production of Deformities by Causing Infection of Bones and Joints, Antiseptic **38**:169-176 (March) 1941.

243. Tunick, I. S., and Stone, J. R.: Friedländer Bacillus Osteomyelitis, Bull. Hosp. Joint Dis. **2**:55-62 (April) 1941.

244. Jensen, D. R.: Chronic Sclerosing Osteomyelitis: Garré, Am. J. Surg. **54**:377-383 (Nov.) 1941.

245. Scheman, L.; Janota, M., and Lewin, P.: Production of Experimental Osteomyelitis: Preliminary Report, J. A. M. A. **117**:1525-1529 (Nov. 1) 1941.

experiments they were able to keep the animals alive for an indefinite period. Rabbits were used, and a preliminary subcutaneous injection was given a week prior to the inoculation of the tibial metaphysis; 0.3 cc. of sodium morrhuate was injected, and one hour following this, 0.2 cc. of a 1:50 dilution of a twenty-four hour broth culture of Staph. aureus was injected into the original metaphysial area.

The authors found that osteomyelitis is invariably produced by this method and that 70 per cent of the animals will live. They therefore feel that further experimentation will be aided by this method of producing the bone infection.

[ED. NOTE: This is an interesting variation and may prove to be of definite practical importance in studying osteomyelitis in animals and human beings.]

Blakemore, Elliott and Hart-Mercer [246] have isolated twenty strains of hemolytic streptococcus using lambs as experimental animals. Fifty-nine cases were studied and 53 cultural growths of hemolytic streptococci were isolated from the suppurative arthritis produced. Intravenous injections into the lambs were followed by sustained bacteremia with periodic intermissions until localization took place. If endocarditis was produced later, this apparently served as a source of continued infection in maintaining bacteremia. It was impossible to infect adult sheep or lambs that had recovered from previous attacks.

In all of the animals dying from joint infections there was found to be marked inflammation of one or more joints, tendon sheaths or bursae, and in 6 of 27 animals endocarditis was present, consisting of streptococcic vegetations, hemorrhages, aggregation of cells and necrotic tissue. These apparently resulted from both emboli and surface implantation and could be compared with acute endocarditis in man.

Suzuki [247] believes that he is the first investigator who has been able to make prolonged studies of experimental pyogenic infection of the bones in guinea pigs. In his series the site of predilection for the hematogenous infection of the bones was not always the metaphysis but sometimes was the diaphysis. In localization of the focus of infection various conditions are of significance. The purulent foci exist more frequently in the metaphysial region if the animals are first brought to a stage of bacterial allergy and thereupon receive injections of small doses of bacilli. This is also true if a sublethal dose is injected into normal animals.

The infection can be more frequently located in the wall of the cortex of the bone if a collodion capsule containing agar and bacilli is placed

246. Blakemore, F.; Elliott, S. D., and Hart-Mercer, J.: Studies on Suppurative Polyarthritis (Joint Ill) in Lambs, J. Path. & Bact. **52**:57-83 (Jan.) 1941.

247. Suzuki, M.: Experimental Studies of Purulent Infection of the Femur and Tibia in Guinea Pigs, Arch. f. klin. Chir. **201**:192-231, 1941.

in the abdomen. The author states that the abscess which develops in the periosteum or at the surface of the bone heals and gives the appearance of an exostosis. The primary disease focus in the cortex, usually involving the superficial layer, although occasionally involving the deeper cortical region, becomes necrotic, and between the necrotic and the normal bone there develops an area of lacunar resorption. An abscess is then formed in the bone in which are found necrotic bone fragments. If the infected emboli involve the entire layer of bony substance, an involucrum with a medullary abscess soon develops, but from his experimental work the author feels that the disease focus is usually located in the superficial areas of bone and that the abscess will according to the virulence of the bacteria and the penetration of the disease process form a cloaca toward the periosteum or the marrow cavity. This course is usually toward the marrow cavity owing to the active callous production of the periosteum. The sequestrum always acts as a germ carrier or inflammatory irritant in the center of the purulent focus. A diffuse medullary phlegmon develops with resorption and osteoporosis of the bone, and finally the abscess again perforates the periosteum. The process is repeated with continued necrosis of bone and formation of involucrum. If the bacilli are attenuated or dead, healing with the formation of cicatricial tissue occurs, or a so-called Brodie's abscess may be formed.

The fate of an abscess arising from the metaphysial medulla varies according to whether there is any direct connection with the epiphysial line, and an abscess springing from this area shows a pathologic nature similar to one arising in the true metaphysial region.

[Ed. Note: The author has written a splendid article, and further experimental observations on involvement of the epiphysial line may shed more light on the growth disturbances so frequently noted in these areas following infection.]

Regional Involvement.—In discussing chronic osteomyelitis of the pelvis, Thomsen [248] reviews a series of 37 cases of tuberculous osteomyelitis and 23 cases of purulent osteomyelitis from the Danish Sickness Insurance Association. Pelvic tuberculosis constituted 1.7 per cent of all skeletal tuberculosis and was found in a decreasing order of frequency in the ilium, the sacrum and the pubic bone. Purulent nontuberculous osteomyelitis of the pelvic ring accounted for 8.1 per cent of all of the cases and was located primarily in the iliac bone near the sacroiliac joint. The differential diagnosis is made from the clinical, roentgen and histologic observations, and it should be kept in mind that in the purulent process giant cells may develop. The author analyzes the prognosis in

248. Thomsen, H.: Chronic Osteomyelitis of the Pelvis, Acta orthop. Scandinav. **11**:307-341, 1940.

tabular form and shows that the prognosis differs for the tuberculous and nontuberculous infections. [ED. NOTE: Tuberculous disease of the pelvis has been found most frequently involving the acetabulum and the sacroiliac joints, but the great majority of osteomyelitis in the body is undoubtedly nontuberculous.]

The Kovens [249] discuss osteomyelitis of the spine treated by fusion with the use of a bone graft and report 5 cases in which the patients were treated by the Albee method. In all of these cases healing was by primary intention, and the authors favor this method over other fusion methods. They stress the fact that the associated abscesses disappeared without surgical drainage and that their resorption was due both to immobilization and to the increase of local vascularity, this causing increased phagocytosis and immune antibodies. [ED. NOTE: Any method producing immobilization of the diseased part will give an opportunity for healing to occur.]

Holmberg,[250] in discussing septic spondylitis, reports 7 cases, stressing the rare incidence of this infection and suggests that its recognition may become more frequent once its diagnosis becomes less confused with that of tuberculous spondylitis. Staphylococcus or mixed infections of Staph. aureus, Staphylococcus albus and Staphylococcus citreus as well as streptococci and other organisms have all been found to be causative agents. In 74 per cent of the cases the patients were male; 47 per cent of the infections were in the lumbar region and 31 per cent in the dorsal region. There is usually a history of trauma, and the author quotes Iselin, who believes that staphylococci may remain dormant in healthy bone but that they will regain their virulence when there is a vitamin C deficiency.

In 58 per cent of the cases reported in the literature the vertebral arches alone were involved; in 34 per cent the vertebral bodies alone were involved, and both regions were affected in 7 per cent. The ages of the patients reported were 11, 13, 14, 28, 33, 35 and 54 years. The author does not feel that there is evidence enough to prove that trauma is an important causative factor, and in 4 of his reported cases spontaneous healing took place without treatment. Roentgenograms are an aid to early diagnosis because they show shadows of abscesses and soft tissue edema; in 1 of his cases this soft tissue swelling was demonstrated only seven days after the patient became ill.

Treatment consists of incision and drainage with immobilization of the affected part, and the author believes that curettage is unnecessary in most cases. Immobilization is important in the treatment of this

249. Koven, B., and Koven, M. T.: Osteomyelitis of Spine Treated with Fusion by Bone Graft, Am. J. Surg. **53**:13-31 (July) 1941.

250. Holmberg, L.: Septic Spondylitis: Report of Seven Cases, Acta chir. Scandinav. **84**:479-504, 1941.

condition. In all 7 cases healing occurred, leaving limitation of motion of the affected part.

[Ed. Note: This interesting report of nontuberculous osteomyelitis of the vertebrae calls attention to the value of a careful examination. Clinically, in these cases there may be simulation of a tuberculous process to some extent, but the roentgenograms show bone proliferation about the area of destruction, and this is characteristic of a mixed or nontuberculous infection. The idea advanced that relighting of a dormant infection may be due to a vitamin C deficiency is interesting.]

Fridmanas,[251] in discussing hematogenous osteomyelitis of the neck of the femur in children, points out the frequent complication of pathologic luxation or subluxation of the coxofemoral joint as well as the difficulty of early diagnosis. All of his patients were admitted to the hospital late and showed extensive destruction at the coxofemoral region. He advocates aspiration of the joint to prevent luxation in the early stages, and if the process has advanced to a sequestration of the femoral head, he feels that the head should be removed surgically and the neck or the greater trochanter placed in the acetabulum and held there by plaster fixation. Osteomyelitis of the neck of the femur should always be kept in mind in any painful disorders of the hip, and the clinical and roentgen examinations should be carefully made to avoid an incorrect diagnosis, which was made in all 4 cases that the author reports. [Ed. Note: It seems that the correct diagnosis should not have been missed in all 4 cases.]

Dalton [252] compares the osteomyelitis occurring in the mandible with that occurring in the long bones and notes some of the differences. In 1 case complete sequestration of the jaw without regeneration occurred. He reports 3 cases.

Penhale [253] discusses the early diagnosis and treatment of osteomyelitis of the jaws, stating that the infection generally enters the jaw by way of a tooth cavity and that a hematogenous infection is rare. The disease is unusual in children under 10 years of age. The usual course of the disease in the jaw is that the disease slowly spreads from the region of the tooth along the mandibular nerve giving rise to increased pain. He feels that mandibular osteomyelitis rarely develops following extraction of teeth but that if the infection does develop removal of an infected tooth will sometimes eliminate severe osteomyelitis. Early drainage is necessary, preferably intraoral, and the sequestrums must be removed as they occur. When the diagnosis is in

251. Fridmanas, J.: Hematogenous Osteomyelitis of the Neck of the Femur in Children, Medicina, Kaunas **22**:55-78 (Jan.) 1941.

252. Dalton, V. B.: Osteomyelitic Conditions in Mandible, J. Am. Dent. A. **28**:951-956 (June) 1941.

253. Penhale, K. W.: Early Diagnosis and Treatment of Osteomyelitis of Mandible, J. Am. Dent. A. **28**:288-297 (Feb.) 1941.

doubt, conservative treatment should be followed. [ED. NOTE: Loss of bone substance following the infection gives rise to asymmetry and is a distressing complication; therefore, early conservative operation is to be done as the author indicates.]

Silver [254] states that following suprapubic prostatectomy there occasionally develops low grade osteomyelitis of the pelvic bones involving particularly the anterior pelvic girdle with varying degrees of disability. [ED. NOTE: This is a rare complication of prostatectomy but should be kept in mind following an unexplained fever, local swelling and tenderness.]

Wheeler [255] reports 3 cases of a condition diagnosed as Sudeck's atrophy which was proved to be periostitis of the pubic bone. He believes that this periosteal thickening with mottled rarefaction of the bones is not true osteomyelitis, for he was unable to reproduce periostitis of the pubes experimentally in rabbits. He believes that it is secondary to nerve injury with acute bone atrophy and that it is a self-limiting disease which lasts from three months to two years. [ED. NOTE: This condition so closely resembles Sudeck's atrophy that we prefer to consider it as falling under this category.]

Cohn,[256] discussing recurrent pyogenic osteomyelitis, reports a case in which the disease remained dormant for forty-seven years and became active following trauma to the old lesion in the tibia. Culture in this case revealed an attenuated form of Staph. albus which took forty-eight hours to appear in the culture. [ED. NOTE: There seems to be no time limit to the relighting of an old infection.]

Browder and Meyers [257] discuss infection of the epidural space following vertebral osteomyelitis and feel that sometimes when the symptoms of epidural space infection are manifest it is rare to find roentgen evidence of bony changes in the suspected vertebra. They report 14 cases in only 1 of which there was an osseous lesion, yet in 12 of the 14 cases osteomyelitis was demonstrated at operation, at autopsy or at later roentgen examination. Staphylococcus is the usual infecting organism, and surgical drainage should be instituted as early as the condition is recognized. [ED. NOTE: These cases illustrate the difficulty of early diagnosis of infectious spondylitis.]

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254. Silver, C. M.: Pelvic Bone Changes Following Suprapubic Prostatectomy, Bull. Hosp. Joint Dis. **2**:10-20 (Jan.) 1941.

255. Wheeler, W. K.: Periostitis Pubes Following Suprapubic Cystostomy: Three Cases Diagnosed as Sudeck's Atrophy, J. Urol. **45**:467-475 (March) 1941.

256. Cohn, B. N. E.: Recurring Pyogenic Osteomyelitis: Report of a Case with Forty-Seven Year Quiescent Period Between Attacks, Am. J. Surg. **54**:741-743 (Dec.) 1941.

257. Browder, J., and Meyers, R.: Pyogenic Infections of Spinal Epidural Space, Consideration of Anatomic and Physiologic Pathology, Surgery **10**:296-308 (Aug.) 1941.

Boharas and Koskoff [258] report a case of recurring spinal osteomyelitis with an acute epidural abscess. Spinal puncture in this case yielded pus in the epidural sac, and the authors mention that frequently there is a subarachnoid block. No bony change was noted by roentgen examination or at operation in this case, but on the seventh postoperative day a small sequestrum was removed from the wound; to the authors this was indicative of vertebral destruction.

Richardson and Ranking [240] discuss the question of bone infection followed by terminal meningitis and feel that occasionally B. coli is the causative agent.

Butler, Blusger and Perry,[259] in discussing staphylococcic osteomyelitis of the spine, divide the condition into three clinical types.

The first type occurs in children or young adults and is characterized by a sudden onset with symptoms of severe bacteremia. Treatment in these cases is directed toward combating the blood stream infection. The mortality rate is extremely high.

The second type is characterized by a sudden onset with general malaise and pain in the back. An abscess rapidly forms with evidence of pressure on the cord. Meningitis may supervene with fatal results. Drainage of an abscess after laminectomy is probably the best treatment in this type of case.

The third type, the authors feel, is rare and is described as follows: The onset is gradual. The patients are almost always adults. The symptoms are referred to the affected vertebra and often diagnosed as tuberculosis of the spine. The authors report that in 2 cases of this type bone grafting has been done with excellent results.

[Ed. Note:· This seems to be an unnecessary division of nontuberculous osteomyelitis of the spine.]

Therapy.—Dickson, Diveley and Kiene [260] give a preliminary report on the use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in the treatment of subacute and chronic osteomyelitis. Twenty-two cases are discussed in this report, in all of which treatment was by local debridement, implantation of sulfathiazole and closure of the wound. Sulfathiazole was given by mouth at least three days preoperatively to insure a blood level of 4.7 per cent.

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258. Boharas, S., and Koskoff, Y. D.: Early Diagnosis of Acute Spinal Epidural Abscess: Report of Illustrative Case, J. A. M. A. **117**:1085-1088 (Sept. 27) 1941.

259. Butler, E. C. B.; Blusger, I. N., and Perry, K. M. A.: Staphylococcal Osteomyelitis of the Spine, Lancet **1**:480-481 (April 12) 1941.

260. Dickson, F. D.; Diveley, R. L., and Kiene, R.: Use of Sulfathiazole in Treatment of Subacute and Chronic Osteomyelitis, J. Bone & Joint Surg. **23**:516-520 (July) 1941.

The technic of operation is as follows: After a tourniquet is applied, the sinus tract is injected with methylthionine chloride, and the sinus is dissected out. The necrotic bone is then removed, and careful saucerization of the bone and excision of the scar tissue are done. Sulfathiazole (1 to 2 Gm.) is then dusted into the wound by a nasal insufflator. The deep soft parts and the skin are then closed by interrupted sutures, and a dressing is applied with moderate pressure. After this the limb is immobilized in plaster. Sulfathiazole is administered for fifteen days after operation. In 14 (78 per cent) of the 18 cases, healing was by primary union; in 2 cases (11 per cent) healing did not occur, and in 2 cases (11 per cent) it was too early to evaluate results. The average healing period was twenty-three days. In this preliminary report the authors urge a further trial of their method.

[ED. NOTE: This article has attracted a great deal of comment, and we believe that the method is of great practical value.]

Key [261] discusses the early operative treatment of acute hematogenous osteomyelitis and reasserts his belief in early operation in the majority of cases. He delays operation only long enough to combat dehydration, and in addition to local chemotherapy he uses antitoxin in selected cases.

Key,[262] in considering the clinical use of sulfonamide drugs in orthopedic cases, defines four types of patients. First there are those with clean operative wounds; for these the dry sterile sulfanilamide was used in 150 cases, sulfathiazole in 70 cases and a mixture of these drugs in 23 cases in which there were nonoperative infections. Secondly there are those with traumatic contaminated wounds; for these the author feels that the local use of these drugs will lessen the incidence of severity of infection when the wounds are sutured or left open. Thirdly there are those with acute pyogenic infections; these infections are of two types: those of locally infected wounds and the acute hematogenous pyogenic infections, such as osteomyelitis and arthritis. In the infected wounds partial débridement, cleansing of the wound and implantation of sulfathiazole with immobilization of the patient are carried out; in the cases of frank osteomyelitis the drug is given by mouth as well as locally, and early drainage is used. Fourthly there are those with chronic osteomyelitis; the author reports that in 14 of 17 cases of chronic osteomyelitis healing by primary union was effected by the method described by Dickson, Diveley and Kiene.

Wilson [263] reports 33 cases of acute hematogenous osteomyelitis and stresses the fact that there is present a disease of the whole organism

261. Key, J. A.: Early Operative Treatment of Acute Hematogenous Osteomyelitis, Surgery **9**:657-665 (May) 1941.

262. Key, J. A.: Use of Sulfanilamide and Sulfathiazole in Orthopedic Surgery, J. A. M. A. **117**:409-412 (Aug. 9) 1941.

263. Wilson, J. C.: Delayed Operative Treatment of Acute Hematogenous Osteomyelitis, Surgery **9**:666-674 (May) 1941.

and not only a pyogenic infection of the bone. He places his patients in four groups.

In the first are those who were operated on the first seven days of their illness. Of these 62.5 per cent had no metastatic lesions, but 1 out of 4 died. In the second are the patients who were operated on between the seventh and the fourteenth day. Of these 61 per cent had no metastatic lesions, and there were no deaths. In the third are those whose abscesses were drained between the second and the third week from the day of illness. Of these 66.6 per cent had no metastatic lesion, and there were no deaths. In the fourth are those patients who had no operation. Of these 25 per cent died.

He feels that from the high mortality rate in those cases in which drainage was instituted early and in those in which no drainage was instituted that adequate drainage should be done only after the effects of the generalized infection have been overcome.

[ED. NOTE: In general it is felt that conservative operation is the keynote in the treatment of acute osteomyelitis and that radical operation is to be used for chronic osteomyelitis; both are to be aided by local and general sulfonamide therapy.]

Bick [264] reports on 20 cases of hematogenous osteomyelitis and concludes that sulfanilamide and sulfapyridine did not materially affect the course of the process and sounds a word of warning against too much confidence being placed in chemotherapy, feeling that it should never take the place of adequate operation.

Baker [265] compares the results obtained from the use of staphylococcus antitoxin with those obtained from the use of the sulfonamide compounds. In hemolytic Staph. aureus infection the ratio of mature to immature polymorphonuclear leukocytes found in the circulating blood can be used to estimate the degree of toxemia and to determine the need for antitoxin therapy. After skin tests for sensitivity have been given, staphylococcus toxins can be neutralized by staphylococcus antitoxin, and the author advises an initial dose of 20,000 units for those under 10 years of age. This is then followed in four hours with an intravenous dose of from 40,000 to 60,000 units, which should be repeated every twenty-four hours thereafter until the proper ratio of the white blood cells is obtained.

Sulfathiazole is of benefit in treating staphylococcic infections, but the author believes that sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) are contraindicated in the presence of

264. Bick, E. M.: Sulfone Chemotherapy in Hematogenous Osteomyelitis, Surg., Gynec. & Obst. **72**:995-1002 (June) 1941.

265. Baker, L. D.: Acute Osteomyelitis with Staphylococcus Septicemia: Clinical Report on Use of Chemotherapy, and Staphylococcus Antitoxin in Its Treatment, South. M. J. **34**:619-627 (June) 1941.

hemolytic Staph. aureus infections. Staphylococcus toxins can be neutralized in vivo by staphylococcus antitoxin prepared from the toxin produced by Burky's Ha strain of hemolytic Staph. aureus.

Early and adequate drainage of all foci of infection is necessary if the antitoxin therapy is to be effective.

[ED. NOTE: This excellent study that the author has been pursuing over several years is valuable, and we hope similar studies will be reported by other observers.]

Kuhlmann [266] discusses his treatment for acute osteomyelitis in children. He makes an opening into the medullary cavity with a sharp curet and then immobilizes the limb in a fenestrated plaster cast. He has treated 103 children with acute osteomyelitis with a mortality rate of only 3.88 per cent. [ED. NOTE: It is doubtful that there is any routine treatment for use in all cases of osteomyelitis in children, but conservative operation with supportive measures is felt to be the best in general.]

Foley [267] reports 15 cases of acute hematogenous septic arthritis; in 10 of these, treatment was by aspiration and immobilization. In 6 of these cases the condition was due to streptococcus and in 9 to staphylococcus. Aspiration of the joint was done with the patient under anesthesia induced with pentothal sodium, and the author is convinced of the value of this method of treatment. [ED. NOTE: This is a small series of cases, but it demonstrates the feasibility of extreme conservatism.]

Grasso [268] reports 8 cases in which he feels there was spontaneous development of acute hematogenous osteomyelitis. In 5 cases the femur was affected; in 2 the tibia and in 1 the proximal metaphysis of the humerus were affected. The author concludes that immediate operative intervention is dangerous and superfluous, and he advises absolute early immobilization in lightly padded plaster casts. He believes that the abscess should be incised and that any sequestrums that form should be removed several months later.

Wilensky [269] gives a general discussion of osteomyelitis, emphasizing the distinction between the casual general infection and a consequent local bone lesion. He does not feel that there is any scientific evidence

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266. Kuhlmann, K.: Treatment of Acute Osteomyelitis in Children, Deutsche Ztschr. f. Chir. **253**:691-703, 1940.

267. Foley, W. B.: Report on Cases of Septic Arthritis, Proc. Roy. Soc. Med. **34**:657-658 (Aug.) 1941.

268. Grasso, R.: Spontaneous Evolution of Acute Hematogenous Osteomyelitis: Expectant Therapy with Early Mobilization and Minimal Intervention, Policlinico (sez. prat.) **48**:601-617 (April 7) 1941.

269. Wilensky, A. O.: Role of Chemotherapy in Treatment of Acute and Chronic Hematogenous Osteomyelitis, M. Rec. **154**:344-346 (Nov. 5) 1941.

to show that chemotherapy will aid the local lesion. [Ed. Note: One of us (P. C. C.) is not at present committed to only immobilization as a routine practice in the treatment of osteomyelitis. He deplores, however, radical operation in the acute phases of the disease.]

Wilensky [270] reports a case of osteomyelitis of the upper part of the right tibia following paronychia of the left great toe with a positive blood culture. Thrombophlebitis of the saphenous vein over the site of the osteomyelitis developed, and this portion of the vein was ligated and removed. The author points out that this is concrete evidence that the metastatic focus may act as the desseminator of a blood stream infection.

Voznescusky [271] discusses methods of treatment of acute hematogenous osteomyelitis in 414 cases in children. All of the patients were treated by early incision and drainage, and the author feels that when there is a massive involvement of the bone subperiosteal resection of the involved portion should be done if at all possible. He feels that the danger of pseudoarthrosis developing is more hypothetic than real. [Ed. Note: Resection is practical in only a few locations in the body.]

Gutierrez [272] advocates packing the medullary cavity with muscle tissue; in treating chronic osteomyelitis in the humerus he uses the deltoid muscle, and in the femur, the vastus lateralis muscle, feeling that the muscle tissue is well supplied with blood vessels and that for this reason he can avoid necrosis and gangrene. [Ed. Note: Some regions of the body lend themselves particularly well to this method following saucerization, but for other regions impairment of muscle function would result. We believe that adequate operation and use of the sulfonamide drugs will give the most satisfactory results in cases of chronic osteomyelitis irrespective of wound packing with muscle tissue.]

Tait [273] reports 6 cases of osteomyelitis in the small bones of the hands and the feet and 1 in the jaw. In all cases treatment was by high voltage roentgen therapy. Cure was obtained in all but 1 case. The author recommends that 1,000 to 2,000 r be given in the first week. [Ed. Note: It seems that the series is rather small to justify completely the author's conclusions, although undoubtedly roentgen therapy is at times most beneficial.]

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270. Wilensky, A. O.: Excision and/or Proximal Ligation of Extraosseous Thrombophlebitis in Treatment of Acute Hematogenous Osteomyelitis with Positive Blood Culture, Surgery **10**:409-410 (Sept.) 1941.

271. Voznescusky, V. P.: Discussion of Methods of Treatment of Acute Hematogenous Osteomyelitis, Novy khir. arkhiv **46**:22-32, 1940.

272. Gutierrez, A.: Gutierrez Method of Treating Chronic Osteomyelitis, Rev. de cir de Buenos Aires **20**:143-162 (April) 1941.

273. Tait, R. M.: Treatment of Osteomyelitis of Small Bones with X-Ray, Canad. M. A. J. **45**:229-231 (Sept.) 1941.

Penberthy and Weller [274] report 19 cases of acute hematogenous osteomyelitis treated with sulfapyridine or sulfathiazole and early drainage. They believe in relatively early and adequate surgical drainage and in the use of these drugs, which apparently limit the complications of this disease.

The LeCocqs [275] believe that neoarsphenamine is a valuable weapon in combating acute osteomyelitis due to Staph. aureus. They report on 30 patients, all of whom showed positive blood cultures. Twenty-one of these received neoarsphenamine, and of these 24 per cent died, and 76 per cent recovered. Of 9 patients who received no neoarsphenamine 89 per cent died, and 11 per cent recovered. [ED. NOTE: This is an interesting observation, but with such a small series further evidence is needed to substantiate this observation, and it is to be hoped that the authors will report on a larger series.]

Hoyt, Davis and Van Buren [276] treated 8 patients with acute hematogenous osteomyelitis with sulfathiazole given orally but with no operation. The dosages of sulfathiazole was 1 to 1½ grains (0.6 to 0.9 Gm.) per pound per day for two to five weeks in conjunction with fluids, transfusions and the usual supportive measures. The authors advise immobilization of the limbs during the painful stage and feel that the end results following this method were most satisfactory. In only 2 cases was any disability presented, and in only 2 cases was there limitation of function. No deaths occurred. [ED. NOTE: These are interesting observations, and while the series is small, the results are unusually good. We are still awaiting a report on a large series of cases of acute osteomyelitis treated without operation.]

Heberling [277] reviews 201 cases of suppurative arthritis in which two hundred and twenty-one joints were treated with the Willems method of open drainage and active motion. There were 13 deaths in the series. The procedure consists of an incision into the joint and the suture of a soft rubber drain to the capsule with immediate active motion. In this series there were 24 patients with complicating osteomyelitis of adjacent bones. The author feels that to be successful the Willems treatment must be instituted early after the onset of the disease and should be started as soon as the patient awakens from the anesthetic.

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274. Penberthy, G. C., and Weller, C. N.: Chemotherapy as Aid in Management of Acute Osteomyelitis, Ann. Surg. **114**:129-146 (July) 1941.

275. LeCocq, J. F., and LeCocq, E.: Use of Neoarsphenamine in Treatment of Acute Staphylococcus Aureus Septicemia and Osteomyelitis, J. Bone & Joint Surg. **23**:596-597 (July) 1941.

276. Hoyt, W. A.; Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcic Osteomyelitis: Treatment with Sulfathiazole Without Operation, J. A. M. A. **117**:2043-2050 (Dec. 13) 1941.

277. Heberling, J. A.: Review of Two Hundred and One Cases of Suppurative Arthritis, J. Bone & Joint Surg. **23**:917-921 (Oct.) 1941.

Meticulous attention to the postoperative care of these patients is necessary if good functional results are to be expected. [ED. NOTE: It is our experience that the cooperation of the patient necessary to active movement is often lacking.]

Syphilis of Bones and Joints.—Palmer [278] states that congenital osseous syphilis affects infants and that there may develop an inability or disinclination to move one or more extremities, giving rise to pseudoparalysis. Improvements followed treatment with sulfarsphenamine, although there was no improvement demonstrable roentgenologically until the patient had received prolonged arsenic therapy. The clinical entity of Parrot's pseudoparalysis is generally caused by a congenital osseous involvement of the affected part either from the bony lesion itself or from the altered muscles of the extremity.

Buchman and Lieberman [279] discuss the prevalence of syphilis in bones and joints in 119 persons with bone and joint lesions of congenital and acquired syphilis out of a total of 89,000 orthopedic patients seen in the outpatient department over a ten year period. Twenty-five of the total number had congenital syphilis, and 94 had acquired syphilis. The incidence of skeletal syphilis among the patients with syphilis under treatment was 5 per cent. [ED. NOTE: The low percentage of syphilis of the bones and joints seen today is in striking contrast to that of earlier reports.]

McCord [280] presents an analysis of 129 Negro fetuses in all stages of gestation and points out that the characteristic features of advanced congenital syphilis are the typical saw tooth serrations noted at the metaphysial area and that positive reactions to Kahn and Wassermann tests are noted in the mother in 90 per cent of the cases. He feels that it is difficult to diagnose syphilis in a fetus weighing less than 500 Gm. [ED. NOTE: Advanced congenital syphilis is frequently recognized by the roentgen findings at the metaphyses; this is probably the more characteristic and constant feature.]

Ancich de Barrios [281] describes 6 cases of a typical syphilitic infection in infants. They presented no specific stigmas and showed normal serologic and roentgen findings in the first few months of observation.

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278. Palmer, T. M.: Parrot's Pseudoparalysis as Manifestation of Congenital Osseous Syphilis, Urol. & Cutan. Rev. **45**:76-78 (Feb.) 1941.

279. Buchman, J., and Lieberman, H. S.: Prevalence of Syphilis of Bones and Joints: Report of Statistical Study at Hospital for Joint Diseases with a Review of Literature, Arch. Dermat. & Syph. **44**:1-12 (July) 1941.

280. McCord, J. R.: Osteochondritis in Stillborn, Am. J. Obst. & Gynec. **42**:667-676 (Oct.) 1941.

281. Ancich de Barrios, E.: Atypical Syphilitic Osteopathies in Infants, Rev. chilena de pediat. **11**:720-731 (Nov.) 1940.

Later, however, syphilis with periostitis and osteomyelitis was confirmed. The author mentions that Epstein has distinguished two forms of osteomyelitis, the central and the peripheral form. The author feels that normal serologic and roentgen findings in the early months of life do not exclude the possibility of syphilis and urges prenatal treatment of the mother. [ED. NOTE: This is a difficult diagnosis to make for infants, and the absence of evidence of bony lesions in roentgenograms may be due to the probability that the soft tissue infection precedes the bone infection.]

Myositis.—McNally and Case [282] report a case of echinococcic cyst of the psoas muscle in a man of 47 and give a review of the literature. Their patient complained of pain low in the back and a mass in the left psoas muscle region which increased in size. On pathologic examination this proved to be an echinococcic cyst. This patient spent the first eleven years of his life in Italy, but no definite clue could be found as to the source of the infection.

Fungus Infection.—Moseley [283] reports a case of actinomycosis in a boy of 17 who gave a history of frequent chewing of grass and leaves. A progressively increasing swelling in the interscapular region with fluctuation of the mass developed, but the roentgenograms showed no lung involvement. Aspiration of the pus showed actinomycosis, and it was felt that this infection probably had entered the body by way of a tooth canal because the patient had recently had an infected tooth removed. The entire fluctuating mass was removed without opening the abscess, and the patient recovered. The value of adequate diet and general constitutional treatment along with iodides and vaccine therapy is stressed, and the author believes that local application of 20 per cent thymol solution was of value following operation.

Nunes d'Almeida [284] reports a case of symmetric actinomycosis of the feet in a man of 49. For the past twelve years this patient had suffered from rheumatism, and roentgenograms revealed destruction of some of the bones of the feet and decalcification of others. Tuberculosis and actinomycosis were both suspected, but the latter was proved histologically, and the patient was given large doses of potassium iodide and radiotherapy. Slow healing and cicatrization resulted. [ED. NOTE: The chronicity of the lesion is striking. Actinomycosis involving the feet is particularly rare.]

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282. McNally, A., and Case, J. B.: Echinococcus Cyst of Muscle: Report of a Case Occurring in Left Psoas Muscle, Am. J. Surg. **51**:419-422 (Feb.) 1941.

283. Moseley, H. F.: Unusual Case of Actinomycosis, J. Bone & Joint Surg. **23**:359-366 (April) 1941.

284. Nunes d'Almeida, A.: Symmetrical Localization of Actinomycosis in Bones of the Feet, Lisboa med. **17**:739-751 (Dec.) 1940.

VIII. CHRONIC ARTHRITIS

General Considerations.—Numerous articles have been written during the past year stressing the general constitutional nature of rheumatoid arthritis and the need for treating it as such.[285] The laboratory findings of Block, Buchanan, and Freyberg,[286] which suggest that jaundice may help because of the concomitant extremely high levels of lipids, phospholipids and cholesterol, are of special interest. The ruling out of arterial disease is of value,[287] but the greatest interest attaches to the general emphasis on the need for treating the individual patient and all his abnormalities of metabolism and function, including his nervous and emotional idiosyncrasies. As Pemberton and Scull [288] say, recovery may be definitely hastened if every disability is considered and every pathologic aspect noted. The problem should include every deviation from normal which is to be found.

> Certainly to deny to the struggling arthritic correction of these several deviations because the whole story is not understood and because no one of the factors involved alone induces or "cures" the disease, is to fail to see the problem in the light of all that modern medicine affords.

Infection as a Causative Factor.—There is nothing new to report on the subject of infection as a causative factor of chronic arthritis. The two

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285. Kelchner, C. H.: Clinical Aspects of the Etiology of Chronic Arthritis, Pennsylvania M. J. **44**:1294-1296 (July) 1941. Andrews, K. R., and Muether, R. O.: Effect of Diet on Arterial and Venous Glucose Tolerance Curves in Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:675-681 (Jan.) 1941. Brown, E. E., and Wasson, V. P.: Capillary Resistance in Rheumatic Children, J. Pediat. **18**:328-336 (March) 1941. Spackman, E. W.; Bach, T. F.; Scull, C. W., and Pemberton, R.: Complete Roentgen Ray Studies of Gastrointestinal Tract in Four Hundred Arthritics, Am. J. M. Sc. **202**:68-77 (July) 1941. Westcott, W. I.: Experimental Etiology of Arthritis, Pennsylvania M. J. **44**:1292-1294 (July) 1941. Zeiter, W. J.: The Prognosis of Rheumatoid Arthritis, Cleveland Clin. Quart. **8**:190-197 (July) 1941. Lewis, T. K.: Résumé of Present-Day Treatment of Arthritis, J. M. Soc. New Jersey **38**:391-395 (Aug.) 1941. Traut, E. F.: What Every Occupational Therapist Should Know About Arthritis, Occup. Therapy **20**:87-91 (April) 1941. Matthews, M. W.: Treatment of Chronic Infectious Arthritis, New Orleans M. & S. J. **93**:396-402 (Feb.) 1941. Scull, C. W.: Metabolic Aspects of Arthritis, Pennsylvania M. J. **44**:1286-1291 (July) 1941.

286. Block, W. D.; Buchanan, O. H., and Freyberg, R. H.: Serum Lipids in Patients with Rheumatoid Arthritis and in Patients with Obstructive Jaundice, Arch. Int. Med. **68**:18-24 (July) 1941.

287. Steinbrocker, O., and Samuels, S. S.: The Arterial Circulation of the Lower Extremities in Chronic Arthritis, J. Lab. & Clin. Med. **26**:974-980 (March) 1941.

288. Pemberton, R., and Scull, C. W.: Nutritional Aspects of the Treatment of Arthritis, Am. J. M. Sc. **201**:250-262 (Feb.) 1941.

schools of thought continue to argue for or against infection.[289] Vaccines are less considered now than before. Green and Freyberg [290] make the following statement about much discussed brucellosis and arthritis:

> Arthralgia and other rheumatic symptoms are common in brucellosis and *temporary*, non-purulent joint inflammation may occur. Our data indicate that brucellosis is seldom, if ever, a cause of *chronic* non-purulent joint inflammation.

Fibrositis.—Fibrositis as a diagnosis is much questioned in this country. There is an excellent synopsis on fibrositis in the *Annals of the Rheumatic Diseases,* the official journal of the Empire Rheumatism Council of England, for December 1940, which throws more light on the English conception of the disease. Stockman [291] says:

> The essential pathology of fibrositis is now well recognized and agreed upon. Under irritation from one source or another the white fibrous tissue of the muscles, nerves, fasciae and other fibrous structures undergoes inflammatory hyperplasia in small patches, the affected areas become swollen and oedematous with serofibrinous exudation, the fibroblasts proliferate rapidly, numerous minute new blood vessels appear, and the whole forms a soft, ill-defined, congested little swelling.

Stockman was the originator of the view that ossifying spondylitis originates as periarticular fibrositis.[292] Buckley [293] feels that the reaction of cells of fibrous tissue may result from trauma, chill, allergy or toxemia. The importance of nodules in diagnosis and treatment he feels is exaggerated. Nodules are common enough but are more often symptomless than otherwise. Harman [294] concludes that the diagnosis of fibrositis rests on the natural history of the disease and its response to injections of procaine hydrochloride into the site of the lesion. Gordon [295] feels that

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289. Pilot, I.: Modified Concepts of Focal Infection, Dis. Eye, Ear, Nose & Throat **1**:117-120 (April) 1941. Hendricks, E. M.: The Colon as Focus of Infection in Arthritis, South. M. J. **34**:652-655 (June) 1941. Bach, T. F.: Focal Infection in Rheumatoid Disease, Pennsylvania M. J. **44**:1297-1301 (July) 1941. Gray, J. W.: The Management of Infected Tonsils, Teeth and Sinuses in Arthritis, J. M. Soc. New Jersey **38**:178-181 (April) 1941. Wetherby, M.: Intravenous Streptococcic Vaccine Treatment of Chronic Rheumatoid Disease, Ann. Int. Med. **14**:1849-1857 (April) 1941. Bohan, P. T.: Chronic Arthritis with Special Reference to Etiology and Management, Rocky Mountain M. J. **38**:698-705 (Sept.) 1941.

290. Green, M. E., and Freyberg, R. H.: The Incidence of Brucellosis in Patients with Rheumatic Disease, Am. J. M. Sc. **201**:495-504 (April) 1941.

291. Stockman, R.: The Treatment of Sciatica, Brachialgia, and Occipital Headache, Ann. Rheumat. Dis. **2**:77-82 (Dec.) 1940.

292. Stockman, R.: Ossifying Spondylitis, Edinburgh M. J. **33**:597-605 (Oct.) 1926.

293. Buckley, C. W.: Fibrositis: Some Old and New Points of View, Ann. Rheumat. Dis. **2**:83-88 (Dec.) 1940.

294. Harman, J. B.: Fibrositis and Pain, Ann. Rheumat. Dis. **2**:101-107 (Dec.) 1940.

295. Gordon, R. G.: The Nature of Fibrositis and the Influence of Psychological States upon It, Ann. Rheumat. Dis. **2**:89-99 (Dec.) 1940.

fibrositis represents four different pathologic processes: (1) sudden strain, leading to hemorrhage and the formation of a blood clot which may not be completely absorbed but may become a nodule, which in turn irritates and leads to further attacks; (2) general wear and tear coupled with poor circulation, which leads to the deposition of metabolic waste products and the formation of nodules; (3) chill, leading to local vascular disturbances analogous to those of chilblain with or without nodule formation; (4) psychogenic disturbances, such as worry, which may be responsible for a fibrositic type of pain which is used as a symbol of emotional discontent or may be more marked because the sensorium is oversensitized as the result of some acute emotional disturbance. Chronic emotional disturbances produce endocrine and autonomic disturbances through vegetative controlling centers in the hypothalamic region; these may be followed by fibrositis. Collins [296] states:

> The term fibrositis covers in common usage the aetiologically undefined conditions named myositis, myalgia, non-articular rheumatism, panniculitis, and periarthritis. . . . A high proportion of cases of fibrositis have an obviously noninfective aetiology. . . . Evidence of inflammation caused by infection in the fibrositic nodule is very slender. Leucocytic infiltration is generally absent. Cultures are always sterile. Reactions of connective tissues to various noxious agents are limited in type. No decision regarding the aetiology of the fibrositic nodule can be made on the available pathological data.

Slot [297] emphasizes the frequency of this type of rheumatic disease among industrial workers and the importance of strains of muscles and ligaments of the neck, the arms, the hands, the back, the gluteal region and the feet as predisposing causes. Race [298] reports that the most useful test is that of the sedimentation rate; this was found to be low in 80 per cent of the cases. Laboratory findings suggest that fibrositis may have a gouty basis.

Gout.—Hench [299] has written an excellent paper giving the picture of gout most clearly, with a carefully planned diet free of purines and low in fats. There is nothing new, but the description of the disease is most encouraging. Solomon and Stecher [300] agree with other writers that gout is not a rare disease. They report 79 cases in five years in the

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296. Collins, D. H.: Fibrositis and Infection, Ann. Rheumat. Dis. **2**:114-126 (Dec.) 1940.

297. Slot, G.: Fibrositis Among Industrial Workers, Ann. Rheumat. Dis. **2**:134-140 (Dec.) 1940.

298. Race, J.: Laboratory Findings in Fibrositis, Ann. Rheumat. Dis. **2**:127-133 (Dec.) 1940.

299. Hench, P. S.: Diagnosis and Treatment of Gout and Gouty Arthritis, J. A. M. A. **116**:453-459 (Feb. 8) 1941.

300. Solomon, W. M., and Stecher, R. M.: Gout: A Prevalent Arthritic Disease, Arch. Phys. Therapy **22**:462-466 (Aug.) 1941.

City Hospital, Cleveland. All agree that colchicine should be used. Haden [301] feels that gout is never cured but only alleviated. Oppenheimer,[302] working on hens, reports the fact

> . . . that a solution containing uricase, if injected either intravenously or intramuscularly in hens with a "gouty" or high plasma uric acid concentration, will produce a sharp lowering of the uric acid level. The higher the plasma uric acid level, the greater the uricolytic activity of the enzyme. . . . Although the weekly uricase injections do seem to keep the plasma uric acid level lower in hens on a high protein diet, this work has not been in progress long enough to determine whether the relatively small dosage employed will prevent the appearance of tophi. Even the control hens have not had sufficient time to develop gouty tophi.

Degenerative Joint Disease (Osteoarthritis).—Stecher [303] in a study of Heberden's nodes decides that there are two types, one resulting from trauma, the other idiopathic. They are profoundly influenced by race, sex and age. Sixty-eight families with Heberden's nodes showed that mothers are affected twice as frequently and sisters three times as frequently as the population in general. There is a hereditary tendency. The author feels that these conclusions apply only to Heberden's nodes. Short and Bauer [304] prefer "degenerative joint disease" as a term rather than "osteoarthritis" since pathologic study clearly indicates that the condition is a degenerative process. In their article they give a complete plan of treatment, and they show that there are

> . . . few indications for surgery in the treatment of degenerative joint disease. . . . One is the removal of loose bodies or so-called "mice" from the knee joint if pain, locking or secondary inflammation is caused thereby. Conservative treatment should be given a trial, but if incapacitating symptoms persist and the loose bodies are demonstrable by examination or roentgenograms, removal should be carried out without delay, since the degenerative process may be hastened by their presence. Acute traumatic effusions usually subside with rest and splinting; if they persist, aspiration should be done. Measures to prevent the development of degenerative joint disease or the acceleration of its course, once present, should be obvious to the reader on consulting the list of contributing factors already given. Such measures fall properly into the field of preventive medicine, and constitute one of the responsibilities of both family physician and specialist. In handling fractures and sprains, diseases of the epiphysis, rickets, infantile paralysis and so forth, the physician must bear in mind the possibility of premature development of degenerative joint disease if the joints are left subject

301. Haden, R. L.: Gout, Proc. Interst. Postgrad. M. A. North America (1940), 1941, pp. 259-263.

302. Oppenheimer, E. H.: The Lowering of Blood Uric Acid by Uricase Injections, Bull. Johns Hopkins Hosp. **68**:190-195 (Feb.) 1941.

303. Stecher, R. M.: Heberden's Nodes: Heredity in Hypertrophic Arthritis of Finger Joints, Am. J. M. Sc. **201**:801-809 (June) 1941.

304. Bauer, W., and Short, C. L.: The Treatment of Degenerative Joint Disease, New England J. Med. **225**:145-150 (July 24) 1941.

to unusual strain. Static deformities and postural defects should be corrected as speedily and as completely as possible. Obesity, especially in those approaching middle age, is hazardous to the well-being of the joints, as well as of the other bodily spasm. Repeated joint trauma, whether occupational or recreational, should be advised against. Finally, in a patient with any form of arthritis, the possibility of secondary degenerative changes must always be kept in mind and guarded against, especially if the movements of weight-bearing joints tend to become limited in a position of mechanical strain.

This paper should be read, since the material is far too complete to abstract. Both Bayles and Russell [305] and Bauer [306] agree that degenerative joint disease of the temporomandibular joint is due to trauma of the cartilage. Prognosis is good for functional results. This subject has not been much written about before, so that these articles are interesting. Copeman [307] reports the effect of the use of pneumatic drills in industry: First there is spasm; then small areas of decalcification of bone develop together with disturbances in the blood vessels, conditions affecting the muscles and injuries to the joints. Injury seems to depend on the way the particular joint reacts to vibration. The condition is osteoarthritis dissecans.

Gold Therapy.—The evidence increases each year that gold is the best medical agent in the treatment of chronic rheumatoid arthritis. Hartung and Cotter [308] say

> . . . gold therapy gives a higher percentage of improvement than any form of therapy yet used by us in the treatment of rheumatoid arthritis.

Gardner [309] reports that 70 to 80 per cent of 250 patients with rheumatoid arthritis treated with aurothiodextrose suspended in oil (solganal B oleosum) in two or more courses showed improvement. In 50 per cent of the recent cases and in 30 per cent of cases of over two years' duration cure was effected. Eight and four tenths per cent of the patients had reactions. Smyth and Freyberg [310] feel that gold therapy is valuable

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305. Bayles, T. B., and Russell, L. A.: Temporomandibular Joint in Rheumatoid Arthritis, J. A. M. A. **116**:2842-2845 (June 28) 1941.

306. Bauer, W. H.: Osteoarthritis Deformans of Temporomandibular Joint, Am. J. Path. **17**:129-140 (Jan.) 1941.

307. Copeman, W. S. C.: The Arthritic Sequelae of Pneumatic Drilling, Ann. Rheumat. Dis. **2**:141-146 (Dec.) 1940.

308. Hartung, E. F., and Cotter, J.: The Effect of Gold Sodium Thiomalate Administration on the Bacteriostatic Properties of the Serum in Patients with Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:1274-1284 (May) 1941.

309. Gardner, E. R.: The Use of Gold in Rheumatoid Arthritis, M. Rec. **153**:321-323 (May 7) 1941.

310. Smyth, C. J., and Freyberg, R. H.: Experiences with Gold Salts in the Treatment of Rheumatoid Arthritis, Univ. Hosp. Bull., Ann Arbor **7**:45-47 (June) 1941.

though not always beneficial. Toxicity is a bar at present. McCarty [311] stresses early treatment. Cecil [312] concludes that in the treatment of rheumatoid arthritis gold therapy offers more than any other known remedy.

In the study of gold therapy Sabin and Warren [313] state that experimentally certain inorganic and organic gold compounds of both the aliphatic and the aromatic series have been found to exert a curative effect on arthritis produced by pleuropneumonic micro-organisms in mice. The greater the dose, the more rapid is the disappearance of the arthritis. Arthritis disappeared in 96 per cent of 171 mice treated, but only in 5 per cent of 77 mice treated with other compounds and in 7 per cent of 70 mice untreated. The earlier the treatment, the more rapid is the cure. Rothbard, Angevine and Cecil [314] draw the following conclusions:

1. Gold sodium thiomalate is an effective chemotherapeutic agent in the prevention of arthritis produced by a hemolytic streptococcus in rats. Its effectiveness is less against a more virulent strain of the same culture.

2. Sulfanilamide and sulfathiazole [2-(paraaminobenzenesulfonamido)-thiazole] are more effective in the prevention of this disease than gold.

3. Neither gold nor the sulfonamide compounds cure arthritis once it is established.

4. *In vitro,* myocrysin [gold sodium thiomalate] is bactericidal under anaerobic conditions.

5. A severe renal injury resulting in death has been observed in rats weighing 100 grams after an injection of 20 mgm. or more of gold.

6. Myocrysin protects rats against hemolytic streptococcus arthritis but since the effective dose is so close to the lethal dose, great caution is necessary in its administration.

Hartung, Cotter and Gannon [315] have studied the excretion of gold and report as follows:

1. Following the subcutaneous administration of gold sodium thiomalate in patients with rheumatoid arthritis, metallic gold can be consistently recovered from the urine, and the twenty-four hour excretion determined.

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311. McCarty, A. C.: The Use of Gold in the Treatment of Arthritis, Kentucky M. J. **39**:107-110 (March) 1941.

312. Cecil, R. L.: Gold Therapy in Rheumatoid Arthritis, Proc. Interst. Postgrad. M. A. North America (1940), 1941, pp. 253-258.

313. Sabin, A. B., and Warren, J.: The Curative Effect of Certain Gold Compounds on Experimental, Proliferative, Chronic Arthritis in Mice, J. Bact. **40**: 823-856 (Dec.) 1940.

314. Rothbard, S.; Angevine, D. M., and Cecil, R. L.: The Influence of Gold Sodium Thiomalate on the Prevention of Hemolytic Streptococcus Arthritis in Rats, J. Pharmacol. & Exper. Therap. **72**:164-174 (June) 1941.

315. Hartung, E. F.; Cotter, J., and Gannon, C.: The Excretion of Gold Following the Administration of Gold Sodium Thiomalate in Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:1750-1755 (Aug.) 1941.

2. In two instances the urinary excretion of gold approximate 9 and 17.2 per cent of the intake of gold during the period of observation.

3. Gold was found in the urine from 60 to 300 days after administration of gold sodium thiomalate had been stopped.

4. Gold content of the stool in three instances ranged from 0.22 to 0.65 mg. in twenty-four hours.

5. No gold could be recovered from the saliva in the two instances studied.

6. As far as our observations were extended, the administration of sodium bicarbonate by mouth had no quantitative effect on the excretion of gold in the urine.

This confirms the work of Freyberg and co-workers.[316]

Vitamin D Therapy.—There has been much discussion about the use of highly concentrated vitamin D. Snyder and Squires [317] report on the use of ergosterol activated by the Whittier method (electrical activation of heat-vaporized ergosterol) in 23 cases: 1. Toxicity was only temporary. 2. There was no consistent change in blood calcium. The sedimentation rate indicated little. 3. Weight increased in most cases. 4. Roentgen studies were of no definite value in determining the clinical progress of the disease. 5. The cases had been observed too short a time and were too few to permit drawing definite conclusions. 6. Beneficial influence of psychic effects was ruled out. The authors conclude that the results indicate that this preparation has definite value and that its use is no more dangerous than other accepted forms of therapy; they point out, however, that it is too early to appraise its value. Farley, Spierling and Kraines [318] conclude that when this type of activated ergosterol is administered in adequate doses and for a long time the beneficial effect is sustained and may be permanent. [ED. NOTE: There have been published claims that this product is less toxic in equivalent doses than are other preparations of activated ergosterol. These claims have, however, been questioned.[318a]] Steinberg [319] has found that vitamin E has a favorable effect on primary fibrositis. He suggests that

316. Freyberg, R. H.; Block, W. D., and Levey, S.: Metabolism, Toxicity, and Manner of Action of Gold Compounds Used in the Treatment of Arthritis; Human Plasma and Synovial Fluid Concentration and Urinary Excretion of Gold During and Following Treatment with Gold Sodium Thiomalate, Gold Sodium Thiosulfate and Colloidal Gold Sulfide, J. Clin. Investigation **20**:401-412 (July) 1941.

317. Snyder, R. G., and Squires, W. H.: Follow-Up Study of Arthritic Patients Treated with Activated Vaporized Sterol, New York State J. Med. **41**:2332-2335 (Dec. 1) 1941.

318. Farley, R. T.; Spierling, H. F., and Kraines, S. H.: Five Year Study of Arthritic Patients: Laboratory and Clinical Observations, Indust. Med. **10**:341-352 (Aug.) 1941.

318a. Freyberg, R. H.: Treatment of Arthritis with Vitamin and Endocrine Preparations, J. A. M. A. **119**:1165 (Aug. 8) 1942. Freeman, S.: Irradiated Ergosterol Poisoning, Correspondence, ibid. **119**:968 (July 18) 1942.

319. Steinberg, C. L.: Vitamin E in Fibrositis, Am. J. M. Sc. **201**:347-349 (March) 1941.

primary fibrositis is a metabolic rather than an infectious process. [ED. NOTE: The personal experience of one of us (G. B.) tends to substantiate this report and indicates that the use of natural-occurring alpha tocopherol is attended with the best results.]

Roentgen Therapy.—Popp and Addington [320] report the studies of 24 cases of psoriasis of the nails. In 6 cases the finger nails only were affected; in 18 cases the hands and the feet both were affected. The average duration of the disease was seven years; the shortest was three months and the longest twenty years. The authors' method of roentgen therapy is described. The results are gratifying; there were complete remission in 6 cases and marked improvement in 10, and there was no improvement in only 2. The benefits were lasting for six months to fifteen years. Roentgen therapy is not recommended as a cure, for benefit is at best only temporary; however, it at least helps to overcome disfigurement. Better results were gained in treating the whole hand or foot than just the nails. Smyth, Freyberg and Peck [321] report as follows: In the treatment of rheumatoid arthritis roentgen therapy gave unpredictable and unreliable results, so that treatment except for psychic effect has been abandoned. Significant results were obtained in 74 per cent of 15 patients with spondylitis rhizomelica, which they are studying further. Experience with degenerative disease of joints and nonarticular forms of rheumatism is insufficient to report on as yet. The reason for using roentgen therapy is still a mystery.

Gonorrheal Arthritis.—Davis [322] reports 100 per cent recovery from gonorrheal arthritis without recurrence or joint damage of 15 patients treated by daily intradermal injection of 2 cc. 5 per cent solution of azosulfamide.[323] The safety, the simplicity and the effectiveness of this method cause the author to feel that it will supersede other methods of treatment shortly.

Physical Therapy.—Ober [324] discusses the treatment needed in the different stages of rheumatoid arthritis as follows: In the invasion stage the symptoms are soreness and stiffness in the morning, and the treatment is the avoidance of fatigue. In the acute stage the symptoms are swelling of the joints, spasm and deformity, and the treatment consists

320. Popp, W. C., and Addington, E. A.: Roentgen Therapy of Psoriatic Arthritis, Radiology **36**:98-99 (Jan.) 1941.

321. Smyth, C. J.; Freyberg, R. H., and Peck, W. S.: Roentgen Therapy for Rheumatic Disease, J. A. M. A. **116**:1995-2001 (May 3) 1941.

322. Davis, T. H.: Treatment of Gonorrheal Arthritis with Special Reference to Intradermal Therapy with Neoprontosil, J. Florida M. A. **27**:396-399 (Feb.) 1941.

323. Azosulfamide is disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

324. Ober, F. R.: Physical Therapy in Arthritis, M. Rec. **154**:144-146 (Aug. 20) 1941.

of rest in bed, the application of heat and splints and mild exercise. For the subacute stage the treatment consists of rest and more freedom; in the chronic stage this treatment is to be continued. When the condition reaches the stage of ankylosis, operation is to be performed. Reiley and Knapp [325] corroborate Kling's reports of 1933 and 1935. They report the cases of 40 patients treated with histamine iontophoresis. Great symptomatic relief, especially of acute myalgia, strain and sprain, was obtained.

Surgical Procedures.—Dickson [326] gives two reasons for operation in cases of arthritis: (1) incapacitating disability and (2) necessity of removing a focus of infection which is active. For the disabled operation often means social betterment which makes life more livable. For appraisal two factors are important, namely, the nature of the joint involvement and the extent of the joint damage present. On patients with atrophic arthritis operation should not be undertaken until the joint is reasonably quiescent. On patients with hypertrophic arthritis, operation may be undertaken at this time. The extent of damage determines the type of operation. The three objectives of operation are: relief of pain, correction of deformity and restoration of function. Commonest operations are manipulation, capsuloplasty, synovectomy, arthroplasty and arthrodesis. Synovectomy is an exception; it can be performed when there is still moderate activity. Preston and Hartung,[327] in discussing surgical procedures for arthritic deformities of the knee, give methods of treatment for four types of patients: (1) those with slight flexion contracture, lateral instability and pain on weight bearing, who require osteotomy to correct the deviation in the weight-bearing line; (2) those with moderately severe flexion contractures, who require manipulations, traction and braces; (3) those with severe contracture, who require posterior capsulotomy, and (4) those with the articular surface destroyed, who require arthrodesis of one knee to relieve the weight on the other. The conclusion is that the end results will be good if the method of treatment selected is suitable for the condition present. Closed methods can be used only in the most mild flexion contractures. The authors emphasize simultaneous use of medical and surgical procedures. Swaim [328] continues to emphasize the importance of early adequate rest and splinting for acutely affected joints. They should be

325. Reiley, R. E., and Knapp, M. E.: Symptomatic Relief in Chronic and Acute Arthritides by Histamine Iontophoresis, Arch. Phys. Therapy **22**:288-294 (May) 1941.

326. Dickson, F. D.: The Surgical Treatment of Arthritis, Ann. Surg. **113**: 869-876 (May) 1941.

327. Preston, R. L., and Hartung, E. F.: The Surgical Treatment of Arthritic Deformities of the Knee, S. Clin. North America **21**:593-603 (April) 1941.

328. Swaim, L. T.: Prevention of Deformities in Rheumatoid Arthritis, Proc. Interst. Postgrad. M. A. North America (1940), 1941, pp. 25-29.

supported until the active stage is over, keeping motion by careful exercise. Payr [329] states that marked improvement in most deformed arthritic hands can be expected by prevention of deformity by early splinting with casts and leather apparatus. He describes use of injections followed by correction and casts. Splints are well applied and are described. [ED. NOTE: This article should be read by all those interested.] Magnuson [330] reports a high percentage of free-moving painless joints after thorough removal of degenerated cartilage in cases of degenerative joint disease. The denuded areas are covered by fibrocartilage which serves as a substitute. Removal of the synovia was not found necessary. [ED. NOTE: The procedure described presents a new field for attack on this type of arthritis.] Royle,[331] in treating sacroiliac arthritis with sciatica, reports the cases of 4 who after all other methods of fixation had failed had complete relief with no recurrences after operative fixation. He uses one or two screws as he previously described.[332]

Arthritis in the Armed Forces.—Mester,[333] a surgeon in the Polish army, points out that the problem of rheumatism in the army is different from that in civilian life, for the patients all do work of the same type; they fall in definite age groups; they are usually of a good healthy type, and there is the possibility always of conscious and unconscious simulation of the disease. Acute rheumatic fever is not difficult to diagnose, but early rheumatoid arthritis and nerve conditions like sciatica are more difficult. This is especially true of the latter which the malingerer can easily copy. In reality the chief problem is the matter of distinguishing real from simulated conditions. In the cases of real rheumatism the hope lies in combating the problem in the early stages. Mester stresses the need of early hospitalization and then warns against early discharge. Two principles are fundamental, namely, accurate diagnosis and adequate treatment by specialists.

Psychotherapy.—Wetherby [334] states:

> This [psychotherapy] may be important in many individuals and is a form of therapy unintentionally given with any planned system of treatment. The encouragement of the patient and a hopeful outlook may be factors of great therapeutic

329. Payr, E.: Treatment and Restoration of Totally Crippled Hands in Severe Rheumatoid Arthritis, Arch. f. klin. Chir. **200**:527-545, 1940.

330. Magnuson, P. B.: Surgical Treatment of Degenerative Arthritis, Surg., Gynec. & Obst. **73**:1-9 (July) 1941.

331. Royle, N. D.: Operative Treatment of Chronic Sacroiliac Arthritis, M. J. Australia **2**:421 (Oct. 11) 1941.

332. Royle, N. D.: New Operation for Fixation of Sacroiliac Joint, Australian & New Zealand J. Surg. **5**:160 (Oct.) 1935.

333. Mester, A. J.: Rational Campaign Against Rheumatism in the Army, J. Roy. Army M. Corps **77**:24-28 (July) 1941.

334. Wetherby, M.: Therapeutic Procedures in Chronic Rheumatoid Disease, Journal-Lancet **61**:414-417 (Oct.) 1941.

significance. Faith healing and practices closely allied to them have seemingly benefitted many individuals with chronic rheumatoid disease probably because many patients have exaggerated their complaints out of proportion to the underlying disease process.

IX. INFANTILE PARALYSIS

General Considerations.—During the year of 1941 there was a definite increase of interest manifested by both laymen and members of the medical profession in infantile paralysis with regard to epidemiologic study, prevention, research and early care of patients. The incidence of the disease was generally higher over the whole country than in 1940 and reached epidemic form in many states and communities in the South, the East and the Middle West. The newspaper and magazine publicity given the work of the Australian nurse, Sister Elizabeth Kenny, who is sponsored by the National Foundation for Infantile Paralysis, has brought more and more inquiries to the physician regarding the value and the merits of this early form of therapy. Many encouraging reports were given at medical meetings during the latter part of the year on the use of the Kenny treatment, but few published reports are available in the literature. There is no doubt that the trend which started in 1940 away from absolute, continuous and rigid immobilization of the joints of the extremities in the acute stage of infantile paralysis has increased.

One of the most outstanding contributions from the epidemiologic viewpoint is that of the isolation of the virus from flies. There have been continued reports of the isolation of the virus from the gastrointestinal tract and from sewage, which was first reported in the literature of 1940. Another outstanding contribution reported from two or more sources and confirmed experimentally is that the patient who has had tonsillectomy is more susceptible to the disease than one who has not had this operation, the bulbar form being by far the most common.

Epidemiologic Study.—Trask and Paul,[335] studying the fecal material from patients with infantile paralysis, conclude that the evidence is yet not sufficient to permit the statement that the presence of poliomyelitic virus in sewage is a direct or even an indirect link in the chain which usually, or even occasionally, leads this infectious agent from one person to another. They further state that until more knowledge is available on this complex subject it seems unwise for health officers to introduce new methods of control.

Paul and Trask[336] believe that the poliomyelitis virus is probably transmitted from one person to another by a number of different channels.

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335. Trask, J. D., and Paul, J. R.: Observations on Fecal Examinations in Poliomyelitis, Am. J. Pub. Health **31**:239-244 (March) 1941.

336. Paul, J. R., and Trask, J. D.: Virus of Poliomyelitis in Stools and Sewage, J. A. M. A. **116**:493-497 (Feb. 8) 1941.

They are of the opinion that many infected persons may become convalescent carriers in the first few weeks of their recovery and may even become transient "healthy" carriers. Theoretically there may be other channels in which contaminated food, milk and water or conceivably insects, mammals and birds play a part. The authors feel definitely that water courses polluted with sewage may enter into the transmission of the disease.

[ED. NOTE: These observations are certainly most timely and pertinent to the subject and may be leading to the complete solution of the epidemiologic problem of the disease.]

Paul [337] further states that the real epidemiologic situation may be and is likely to be a complex, conditioned largely by summer weather and aided by rural environment. He believes that the nasopharyngeal portal of entry is unusual in human beings. [ED. NOTE: There is no doubt that the investigations of all workers in this field are pointing away from the nasopharynx and toward the gastrointestinal tract as the portal of entry.]

Sabin and Ward [338] report the case of a woman laboratory worker aged 35 in whom poliomyelitis developed, most likely contracted in the laboratory in which she was working with the virus.

Perkins [339] reports an epidemic of poliomyelitis in Minnesota in 1930 in which there was a definite radial spread of the disease from a central focus in a rural area. Instances are given of the apparent spread through person to person contact. He presents data which suggest possibly that on infection with the poliomyelitis virus male patients are more apt to have involvement of the nervous system and female patients are more apt to experience subclinical attacks. [ED. NOTE: This is an interesting observation, but the statistics on cases in epidemics do not show that male persons are any more often affected than female persons.]

Causation.—Piszczek and others [340] report on a small epidemic in Cook County, Ill. They found the virus in the stools of 6 of 38 contacts; on the other hand, there was none found in 14 control specimens of normal residents in the community. The virus was found in the stools of 2 presumably healthy children who were in contact with adult mem-

337. Paul, J. R.: Poliomyelitis, Bull. New York Acad. Med. **17**:259-267 (April) 1941.

338. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: Distribution of Virus in Nervous and Non-Nervous Tissues, J. Exper. Med. **73**:771-793 (June) 1941.

339. Perkins, J. E.: Apparent Spread of Poliomyelitis Through Four Families, Minnesota Med. **24**:924 (Nov.) 1941.

340. Piszczek, E. A.; Shaughnessy, H. J.; Zichis, J., and Levinson, S. O.: Acute Anterior Poliomyelitis: Study of Outbreak in West Suburban Cook County Illinois; Preliminary Report, J. A. M. A. **117**:1962-1965 (Dec. 6) 1941.

bers of their families who became ill with poliomyelitis. The virus was isolated from a presumably healthy person two months after his contact with persons who became ill with poliomyelitis and one month after contact with his father, who died of poliomyelitis.

Sabin and Ward [341] report investigative studies on the elimination of virus in patients with paralytic poliomyelitis during the first two weeks of the disease as follows: 1. The nasal secretions collected from 22 patients and the saliva and oral secretions expectorated by 20 patients failed to yield a virus. 2. In 10 of these patients the virus was isolated from single specimens of the lower part of the intestinal tract. 3. No virus was found in large amounts of urine obtained from 12 of these patients. 4. Virus was found in 50 per cent of 58 children under 8 years of age and from only 12 per cent of 60 older persons. [ED. NOTE: These statistics are certainly most interesting and are of extreme significance in the study of this disease.]

Sabin and Ward [342] isolated the virus from 5 of 16 flies caught in different sections of Atlanta, Ga., and Cleveland during outbreaks. Similar observations had previously been made by Paul and Trask in two rural areas in Connecticut and Alabama. This evidence certainly suggests that the contamination may have been picked up by the flies in the feces in open privies and certainly gives strong evidence for this mode of transmission of the disease.

Sabin [343] writes that the virus may continue to multiply in the alimentary tract long after the disappearance of the clinical signs of the disease; this is evident from the fact that in some instances the virus has been found to be excreted in the stools for weeks and months after clinical recovery. One instance is recorded in which the virus was found four months after a mild illness of two days' duration.

Fischer, Stillerman and Marks [344] report a high incidence of the bulbar form of infantile paralysis among the patients who had their tonsils and adenoids removed a short time prior to the illness. This was confirmed in the Toronto epidemic of 1937 among the children from 3 to 12 years of age. The authors cite the work of Sabin in which he has shown experimentally in monkeys that the injection of a moderate amount of virus into the tonsillopharyngeal region produced

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341. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: Elimination of Virus, J. Exper. Med. **74**:519-529 (Dec.) 1941.

342. Sabin, A. B., and Ward, R.: Nature of Nonparalytic and Transitory Paralytic Poliomyelitis in Rhesus Monkeys Inoculated with Human Virus, J. Exper. Med. **73**:757-770 (June) 1941.

343. Sabin, A. B.: Olfactory Bulbs in Human Poliomyelitis, Am. J. Dis. Child. **60**:1313-1318 (Dec.) 1940.

344. Fischer, A. E.; Stillerman, M., and Marks, H. H.: Relation of Tonsillectomy and of Adenoidectomy to Incidence of Poliomyelitis with Special Reference to Bulbar Form, Am. J. Dis. Child. **61**:305-321 (Feb.) 1941.

poliomyelitis with involvement of the nuclei of the cranial nerves in 13 of 16 monkeys, while there was involvement of these structures in only 15 of 250 monkeys in which the disease developed after nasal instillation of virus. Sabin concludes that in most of the monkeys the virus entered and reached the nuclei of the cranial nerves along the nerves supplying the tonsillopharyngeal region. Fischer, Stillerman and Marks further conclude that the incidence of the bulbar form of infantile paralysis is twice as great in those patients whose tonsils have been removed at any time previously as in those with tonsils intact. Also cited in this article is a publication of Top and Vaughan reporting on an outbreak in Detroit in 1939 in which bulbar paralysis developed in 27 per cent of patients with their tonsils previously removed as against 4.2 per cent of those with their tonsils intact. In the 23 fatal cases in this epidemic, 20 patients, or 87 per cent, had tonsillectomy performed previous to the onset of the disease. [ED. NOTE: These figures are certainly most significant in the epidemiologic study of the disease.]

Krill and Toomey,[345] in writing on the part which tonsils play in poliomyelitis, conclude that poliomyelitis virus may have been present at the time of the operation in the throats of the children on whom they operated or that the virus may have been introduced after the operation. In the 5 cases which they report they suspect that the virus was not present in the throats when the tonsils and the adenoids were removed and that the virus was introduced later.

Duggan[346] states that it is his belief the pathologic and clinical evidence indicates that poliomyelitis may be due to a histamine-like body, that this body is a product of the body's own cells and that it may be produced by cold or as a result of antigen-antibody combination secondary to infection of the upper part of the respiratory tract. Allergy rather than immunity results. [ED. NOTE: This is a rather interesting observation, but it certainly needs further proof before it can be accepted.]

In his usual thorough way Toomey[347] concludes after a critical review of poliomyelitis that the following events are epochal in the progress of research on the disease in the past forty years: (1) the isolation of the virus from the human being and its transference to monkeys; (2) the demonstration of virus-neutralizing antibodies in the blood serums of convalescent patients with poliomyelitis; (3) the evaluation of the pathologic nature of the disease and the acceptance of the conception that nerve cells are destroyed first and that other

345. Krill, C. E., and Toomey, J. A.: Multiple Cases of Tonsillectomy and Poliomyelitis, J. A. M. A. **117**:1013 (Sept. 20) 1941.

346. Duggan, W. F.: Anterior Poliomyelitis: Manifestation of Acute Tissue Anoxia, New York State J. Med. **40**:1780-1787 (Dec. 15) 1940.

347. Toomey, J. A.: Poliomyelitis: Critical Review, J. Pediat. **19**:103-130 (July) 1941.

phenomena follow; (4) the demonstration that the virus spreads along neurons to the central nervous system; (5) the discovery that the virus can be acclimated to some smaller laboratory animals, and (6) the fact that the virus can be easily isolated from the stools of patients who have had the disease.

Pathologic Characteristics.—Peers,[348] comparing the lesions produced in the brain of man and monkey with a Lansing strain of virus, concludes that the lesions in the human brain agree in all essential details of type and distribution with those in a number of other brains from patients with poliomyelitis being studied in the laboratory. It was thought that generally the disease in the brain infected with the Lansing strain seemed anatomically rather less severe than that observed in other human specimens. The pattern of the fully developed disease was essentially identical in man and monkey, though the route of inoculation was obviously different.

Hipps,[349] reporting on his pathologic studies of muscle tissue in cases of anterior poliomyelitis, has certainly made a most worth while contribution to this part of the subject. He studied sections of various muscles during different stages of the disease. Gross pathologic examination of the muscles showed atrophy, degeneration and fibrous and fatty tissue replacement. There were zones of fibrofatty degeneration with good muscle above and below. The fatty change was nearly always the greatest near the musculotendinous junction. The muscles would not contract when pinched. They had no elasticity; they would stretch but when stretched would not return to their former length. These muscles were usually graded 0 on clinical examinations. The author is of the opinion that the results of physical therapy during his experience during the past fifteen years were definitely disappointing and that nature had more to do with the return of muscle power than physical therapeutists. He concludes by speculating on the possibility of improving muscle power by taking small strips of fascia lata and using these as mattress sutures to go between the belly of a good muscle across the fatty zone to the tendon below. He also brings up the question of injecting a sclerosing solution into this fatty zone between the good muscle and the tendon in order to form a strong fibrous mass which would effectively transmit the pull of the good segment above. [ED. NOTE: This is an interesting and important pathologic study.]

Sabin and Ward[338] conclude that the pattern of virus distribution in human poliomyelitis points to almost the entire alimentary tract as a primary site of attack by the virus and contains no support for the

348. Peers, J. H.: Poliomyelitis Induced by Lansing Strain of Virus: Comparison of Lesions in Man and in Monkeys, Arch. Path. **32**:928-938 (Dec.) 1941.

349. Hipps, H. E.: Muscle Pathology in Anterior Poliomyelitis in Relation to Function, South. M. J. **34**:135-146 (Feb.) 1941.

concepts involving either the olfactory pathway or the respiratory tract. The demonstration of virus in the abdominal sympathetic ganglions of 1 patient is significant in suggesting one of the possible routes of virus progression in certain instances. Pathologic studies on a large number of tissues obtained from patients who died have revealed that the virus is predominantly distributed in certain regions of the nervous system and in the alimentary tract.

Experimental.—Bodian and Howe [350] report on experimental work in which successive interruption of the nerve fibers of the sciatic nerve was performed by transection or freezing at intervals of two or three weeks at least three times. They found that the anatomically intact nerve fibers of the central stump as well as the incompletely regenerated fibers in the peripheral stump are rendered incapable of transmitting the poliomyelitis virus to the central nervous system. When a considerable number of fibers have completed their regeneration, however, that is, after at least two months have elapsed following the last nerve fiber interruption, inoculation of the central stump results in poliomyelitis. They conclude that the metabolic changes induced in neurons or their axons prevent infection by inoculation of the nerve central to the points of interruption, even when the virus of poliomyelitis is placed in direct contact with every axon. It is therefore highly probable that the axon protoplasm is the active transmitter of the virus in the nerve. When this protoplasm is sufficiently altered in its metabolism by the successive distal injuries and the resulting regenerative efforts, it is definitely refractory to the virus.

Sabin and Ward [342] write on the nature of nonparalytic and transitory paralytic poliomyelitis in monkeys inoculated with human virus. The term "nonparalytic poliomyelitis" has been used with reference to human beings to designate those who in addition to having the normal signs and symptoms of infantile paralysis, starting with headache, fever, vomiting and sore throat, have stiffness of the neck and the back, pleocytosis, tremor and other signs and symptoms of preparalytic poliomyelitis but in whom paralysis never develops. These patients show the virus in the stools. The authors have demonstrated the nonparalytic form in monkeys. In this infection there is a destruction of an appreciable number of nerve cells in the spinal cord; in the experiments, however, there was a failure of the process to progress which the authors feel was due to equilibrium between the host and the virus. The transitory character of the paralysis in some monkeys may have depended in part on the fact that apparently normal function can be carried on with less than the normal number of nerve cells and on the possibility

350. Bodian, D., and Howe, H. A.: Experimental Studies on Intraneural Spread of Poliomyelitis Virus, Bull. Johns Hopkins Hosp. **68**:248-267 (March) 1941.

that not all nerve cells attacked by poliomyelitis virus are irreversibly damaged. [Ed. Note: This is another interesting study which may explain the absence of paralysis in patients associated with epidemics who have all the other signs and symptoms of the disease.]

Trask and Paul [351] have demonstrated that the green African monkey can be infected with the poliomyelitis virus as well as the Indian or rhesus monkey. This is the first time that monkeys other than rhesus monkeys have been infected.

Clinical Findings.—McDaniel [352] reports some interesting facts about the epidemic in South Carolina in 1939. The white and the Negro races were apparently equally susceptible. Eighty per cent of the cases in one county and 95 per cent of the cases in the other counties in the state were of the paralytic form. There were 35 deaths (7.9 per cent) in the total epidemic. The incidence of the epidemic extended over a six months' period from April to September. In this epidemic virus was recovered from sewage for the first time, and the cotton rat was able to be infected with the virus.

Plastridge [353] points out the dangers of habit limps in patients with infantile paralysis and points out some methods of prevention. Supervised instructed walking should make the gait smooth, steady and inconspicuous, make the gait as rapid as possible, with safety to the person and to the weakened muscles and make the walking not merely an expedient means of locomotion but a constant corrective training toward normal walking. [Ed. Note: This is a valuable contribution. More attention should be paid to this by physical therapeutists and orthopedic surgeons. There is no doubt that a great many of the unsightly gaits of infantile paralysis could be prevented if more attention were paid to the early stages of walking after the paralysis.]

Kleinberg and Horwitz [354] made a study of the obstetric experiences of women who have had infantile paralysis. Their material consisted of 243 paralyzed women. They call attention to the following four types of deformity of the pelvis: (1) lateral pelvic obliquity; (2) increased anterior pelvic tilt with exaggerated lumbar lordosis; (3) anteroposterior axis deviation or rotation about a longitudinal axis, and (4) rotation of one innominate bone on the other innominate bone about a transverse axis, or torsional deformity. They conclude that a normal or

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351. Trask, J. D., and Paul, J. R.: Experimental Poliomyelitis in Circopithecus Aethiops Sabaeus (Green African Monkey) by Oral and Other Routes, J. Exper. Med. **73**:453-459 (April) 1941.

352. McDaniel, G. E.: Preliminary Discussion of Poliomyelitis in South Carolina in 1939, J. South Carolina M. A. **36**:331-336 (Dec.) 1940.

353. Plastridge, A. L.: Gaits, Physiotherapy Rev. **21**:24-29 (Jan.-Feb.) 1941.

354. Kleinberg, S., and Horwitz, T.: Obstetric Experiences of Women Paralyzed by Acute Anterior Poliomyelitis (with Special Reference to Pelvic Deformities), Surg., Gynec. & Obst. **72**:58-69 (Jan.) 1941.

uneventful pregnancy and labor with normal offspring is to be anticipated for these patients and that there is no indication for the interruption of the pregnancy at any stage.

Boyd [355] reports the presence of renal calculi in bedridden patients with poliomyelitis. He feels that the patient's position should be changed frequently and as completely as possible and that the patient should lie on the abdomen an hour or two at a time every day, beginning as soon as his paralysis and his general condition will permit. This condition is reported in 3 patients with infantile paralysis. [ED. NOTE: This is a sensible suggestion and should be carried out in every clinic.]

Nonoperative Treatment.—Levinson and Wolf [356] report on the use of immune serum in the treatment of infantile paralysis. They have used this serum extensively for the last ten years and feel that their results are encouraging. It has been used on 400 patients in the preparalytic stage, and the authors conclude that the incidence of moderate paralysis in this group is 4 per cent and that it is rare for severe paralysis to appear if serum treatment is started early in the disease. They believe that if the serum is given to paralyzed patients during the acute stage with the paralysis spreading that it may have some effect in checking the progression of the paralysis. They present no control untreated group for comparison. [ED. NOTE: Poliomyelitis immune serum is generally thought now to have little value in spite of this report to the contrary.]

Irwin,[357] writing on the early orthopedic care of the patient with poliomyelitis, gives his impressions of what has been considered the orthodox care during this stage, namely, that exercises should not be started until the improvement from immobilization ceases and that when these exercises are started they are best done in a warm water pool. This should be continued for three or four months before weight bearing is allowed if paralysis is in the legs. The author emphasizes the importance of complete rest during this early convalescent stage and that the exercises increase the muscle power by hypertrophy of the muscle tissue.

Hipps [358] reports on the care of 88 patients treated in the Crippled Children Hospital, Marlin, Tex., over a period of two and a half years.

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355. Boyd, M. L.: The Formation of Renal Calculi in Bedridden Patients, J. A. M. A. **116**:2245-2247 (May 17) 1941; The Significance of Sensory Paralyses in Poliomyelitis Patients in Whom Renal Calculi Develop, J. Urol. **45**:647-651 (May) 1941.

356. Levinson, S. O., and Wolf, A. M.: Human Serum: Its Application in Medicine, M. Clin. North America **25**:219-243 (Jan.) 1941.

357. Irwin, C. E.: Early Orthopedic Care in Poliomyelitis, J. A. M. A. **117**: 280-282 (July 26) 1941.

358. Hipps, H. E.: Muscle Behavior Following Infantile Paralysis, Am. J. Surg. **53**:314-318 (Aug.) 1941.

In some of these cases the condition was in an early stage, and in some it was in a late stage. The author concludes that muscles long paralyzed lost strength much more often than they gained strength if treated in a relaxed position for six to twelve weeks; that muscles which were graded zero, trace or poor and had been paralyzed as long as three months showed no appreciable gain on physical therapy treatment; that muscles which were graded poor plus, fair and good showed a considerable and justifiable improvement with physical therapy; that the age group 6 to 16 years showed a greater improvement than younger or older groups, and that the patients who received early careful physical therapy showed much better muscle recovery than those treated otherwise. [Ed. Note: This is an interesting study, but the number of cases is too small to make it of much value.]

Over a four year period McCarroll and Crego [359] studied 160 cases of recent infantile paralysis treated with various types of treatment. They conclude that since the type of early treatment has little or no effect on the course of the disease this does not alter the degree of residual paralysis which is seen. They believe that the orthopedic measures probably alter little, if at all, the course of the disease and that the residual involvement is primarily dependent on the degree of initial paralysis and the amount of actual destruction which has taken place in the cells of the anterior horn. They further believe that immobilization and protection are indicated for the comfort of the patient during the acute stage, the prevention of deformities and the prevention of stretch paralysis in the involved muscles. [Ed. Note: This report has caused a great deal of comment and definitely contraindicates a great deal of prolonged physical therapy.]

Cole and Knapp [360] give the first report on the patients treated by Sister Kenny herself at the Minneapolis General Hospital and under the direction of the orthopedic and physical therapy departments of the University of Minnesota Medical School. In this report they simply give impressions. Since this time a great many accurate studies have been reported from this clinic. They conclude that certainly harm has not resulted to any of the observed patients under Miss Kenny's care from the abandonment of immobilization.

[Ed. Note: There is certainly nothing in recent years that has caused more comment, favorable and unfavorable, on any one orthopedic subject than the principles as laid down for the early care of the patient

359. McCarroll, H. R., and Crego, C. H., Jr.: Evaluation of Physiotherapy in Early Treatment of Anterior Poliomyelitis, J. Bone & Joint Surg. **23**:851-861 (Oct.) 1941.

360. Cole, W. H., and Knapp, M. E.: Kenny Treatment of Infantile Paralysis: Preliminary Report, J. A. M. A. **116**:2577-2580 (June 7) 1941.

with poliomyelitis by Elizabeth Kenny. Most observers who have watched her work and studied her methods are of the opinion that the results obtained are better than those obtained with the present orthodox method of care. No sound scientific reason which has been generally accepted has been given to explain these results. Many odd statements have been made by scientific persons without adequate basis or explanation. There is no doubt that a great deal of good will come from the discussions of this treatment and that our present orthodox methods are going to be altered to a considerable extent in the next few years. The time, the expense and the special training necessary for the workers employing the Kenny method may make the universal application of this treatment an impossibility for some time to come.]

Wilson [361] reports on the value of respirators in the treatment of poliomyelitis. Of 331 patients with infantile paralysis treated in respirators 150, or 45 per cent, died. In the 150 fatal cases 127 were patients reported as having the bulbar form of the disease or as having difficulty in swallowing. Of 204 patients with bulbar poliomyelitis 127 died—a mortality rate of 67 per cent; of the 127 patients with nonbulbar poliomyelitis 23 died—a mortality rate of 19 per cent. Many of the patients who died were in the respirators only a short time and probably could not have been expected to be materially helped. The impressions received from this article are that the use of a respirator for poliomyelitis is generally disappointing and that experience with this piece of apparatus certainly does not realize the high expectations for saving lives which were originally entertained. [ED. NOTE: It is the opinion of one of us (A. R. S.) that these conclusions are exactly right. If the opinion of Sister Kenny about respirators is correct, there will be no further need for them.]

Operative Treatment.—Eaton [362] reports the results of abdominal stabilization in the treatment of infantile paralysis. He found that in only 25 per cent of the cases in a small series was there increased power in the partially paralyzed abdominal wall muscles; that it is true that in 50 per cent of the cases there was marked improvement in the stabilization of the trunk on the pelvis; that in the presence of a developing scoliosis the operation appeared to be effective in arresting the progress of the deformity, and that the most striking benefit has been the patient's improvement in general physical well-being, the broadening of the activities, the increase of endurance and the lessened tendency to fatigue.

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361. Wilson, J. L.: Symposium on Poliomyelitis: Use of Respirator, J. A. M. A. **117**:278-279 (July 26) 1941.

362. Eaton, G. O.: Results of Abdominal Stabilization in Poliomyelitis, South. M. J. **34**:443-445 (April) 1941.

X. NEUROMUSCULAR DISORDERS, EXCLUSIVE OF INFANTILE PARALYSIS

Neurologic Injuries of the Spine.—In the past year much has appeared in the literature concerning injuries of the spine and the peripheral nerves. This is probably accounted for in part by the war. Harley [363] describes the various types of war injuries and wounds of the cord and the cauda equina. Dittrich [364] brings out the importance of damage to the epidural fat in producing neural symptoms in bullet wounds of the spine. Antonucci [365] describes the types of wounds and injuries of the cord and spinal nerves associated with vertebral injuries, and Gowlland,[366] the after-treatment of paraplegia in cases of wounds of the spine. Two articles, those by Jakob and associates [367] and Kankat,[368] describe complications of injuries due to compression of the spinal cord, such as painful spastic paraplegia and paralysis of the bladder and the rectum.

Injuries to the Peripheral Nerves.—With regard to the peripheral nerves attention is drawn to almost all of the joints in the body and the nerve injuries complicating wounds and other injuries of these joints. Hyslop [369] describes the complications of ankle sprain, and Isenschmid and Rieben [370] describe the sciatic lesions in cases of traumatic dislocation of the hip. Thompson [371] discusses paralysis of the serratus muscles complicating dislocation of the shoulder, and Dieulafé [372] paralysis of the median nerve complicating supracondylar fractures of the

363. Harley, H. R.: Notes on War Injuries of Spinal Cord and Cauda Equina, Guy's Hosp. Gaz. **55**:41-43 (Feb. 22) 1941.

364. Dittrich, R. J.: Spinal Injury (Bullet Wound): Role of Epidural Fat in Producing Neural Symptoms; Report of Two Cases, J. Kansas M. Soc. **42**:65-69 (Feb.) 1941.

365. Antonucci, C.: Lesions of Spinal Cord and of Spinal Nerve Roots in Vertebral Injuries, Arch. ed atti d. Soc. ital. di chir. **43**:153-296, 1937.

366. Gowlland, E. L.: After Treatment of Paraplegic Patients Following Injuries to Spine, Brit. M. J. **1**:814-815 (May 31) 1941.

367. Jakob, C.; Prini, I.; Riedel, C., and Thenon, J.: Painful Spastic Paraplegia Due to Compression of Lower Dorsal Spinal Cord by Dural Psammoendothelioma: Case with Improvement After Surgical Therapy, Semana méd. **2**:1387-1394 (Dec. 19) 1940.

368. Kankat, C. T.: Compression of Spinal Cord Due to Old Spinal Fracture: Paraplegia and Paralysis of Bladder and Rectum: Results of Surgical Intervention, Türk tib cem. mec. **6**:338-350, 1940.

369. Hyslop, G. H.: Injuries to Deep and Superficial Peroneal Nerves Complicating Ankle Sprain, Am. J. Surg. **51**:436-438 (Feb.) 1941.

370. Isenschmid, R., and Rieben, G.: Lesions of Sciatic Nerve in Traumatic Dislocations of the Hip, Schweiz. med. Wchnschr. **71**:137-141 (Feb. 8) 1941.

371. Thompson, G. C. V.: Paralysis of Serratus Anterior Muscle Complicating Dislocation of Shoulder, M. J. Australia **1**:231-232 (Feb. 22) 1941.

372. Dieulafé, R.: Paralysis of Median Nerve After Supracondylar Fracture of the Humerus: Case, Mém. Acad. de chir. **66**:703-706 (Oct. 16-30) 1940.

humerus. DeRabinovich [373] calls attention to the late appearance of ulnar paralysis after injury or wounds about the elbow.

In connection with injuries of the peripheral nerves in general Deery [374] outlines a number of different operative procedures for repair of injuries to the peripheral nerves in a rather complete listing of methods. Rogers [375] shows good results which may be obtained by the treatment of injuries of the peripheral nerves with amnioplastin (dried and sterilized amniotic membrane). Platt [376] describes wounds and injuries of nerves in general in a symposium on the sequelae of war wounds.

An article by Homans [377] describes minor causalgia of different nerves following injuries and wounds, and Hurst [378] draws attention to hysterical contractures following injuries in war.

It may be seen, therefore, that there is a constantly increasing flow of material concerning the traumatic conditions of nerves; this will undoubtedly become further augmented in the coming year.

Cerebral Palsy.—In the field of cerebral palsy there is also a wider distribution of literature than previously. An article by Putnam [379] details a careful distinction between the neurologic aspects of spasticity and athetosis. Wolf, [380] in considering the therapy of hemiplegia both of cerebral palsy and poliomyelitis origin, points out that it is important to determine the presence of contractile muscle if any attempt to obtain return of power is expected to be made. Electrical reactions in patients with poliomyelitis will allow the selection of suitable subjects with reasonable certainty. The author feels that the use of long wave diathermy often brings about definite improvement in some of the cases in which the condition has been present a long time. Norfleet, Raney and Baker [381] discuss the major types of cerebral palsy, namely, spasticity,

373. de Rabinovich: Late Ulnar Paralysis After Injury to the Elbow: Cases, Rev. neurol. de Buenos Aires **5**:122-131 (April-June) 1940.

374. Deery, E. M.: Injuries to Peripheral Nerves, S. Clin. North America **21**:469-483 (April) 1941.

375. Rogers, L.: Experiences in Treatment of Peripheral Nerve Injuries with Amnioplastin, Brit. M. J. **1**:587-589 (April 19) 1941.

376. Platt, H.: Symposium on Sequelae to War Wounds: Sequelae to Nerve Injuries, M. Press **205**:371-373 (May 7) 1941.

377. Homans, J.: Minor Causalgia Following Injuries and Wounds, Ann. Surg. **113**:932-941 (June) 1941.

378. Hurst, A.: Hysterical Contractures Following Injuries in War, Clin. J. **70**:29-40 (Feb.) 1941.

379. Putnam, T. J.: Neurologic Aspects of Spasticity and Athetosis, New York State J. Med. **41**:1822-1827 (Sept. 15) 1941.

380. Wolf, H. F.: Treatment of Fresh and Old Cases of Hemiplegia and Poliomyelitis by Physical Therapy, M. Rec. **153**:263-265 (April 16) 1941.

381. Norfleet, G. M.; Raney, R. B., and Baker, L. D.: Neurologic Orthopedic and Therapeutic Aspects of Cerebral Palsy, North Carolina M. J. **2**:236-242 (May) 1941.

athetosis, incoordination and tremor, and the pathologic changes and the physical differentiation of the types. They describe also the establishment of the cerebral palsy unit at the Duke University School of Medicine and outline briefly some of the principles of treatment. Gustafson and Garceau [382] have statisticized 185 cases of cerebral spastic paralysis and point out that the proper management of labor is a factor in the prevention of the condition. They feel that premature labor is the greatest single factor in the causation of cerebral palsy and conclude that many cases of cerebral spastic paralysis may occur when labor has been thoughtlessly managed. Boorstein [383] gives a summary of the general problem of the child with cerebral palsy both from the mental and from the physical point of view, concluding that the Binet-Simon method of intelligence testing is not entirely adequate and discussing to some extent the various causative factors. He points out the inadvisability of operation on patients with athetosis and states that operations should be limited exclusively to patients with spastic cerebral palsy. Brander [384] describes the heredity of congenital spastic hemiplegia, and Haldane,[385] partial sex linkage of recessive spastic paraplegia. Jakob and Scaravelli [386] describe deaf-mutism and familial spastic quadriplegia in 7 brothers and a sister. The three aforementioned articles are interesting because of their demonstration of the hereditary factors sometimes seen in certain types of spastic paralysis. Phelps [387] has presented a series of articles concerning different phases of the control of spastic paralysis. One article describes the differential characteristics; another, the rehabilitation; a third, factors influencing treatment, and the fourth, the correlation between physical therapy and occupational therapy in the treatment of the condition.

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382. Gustafson, G. W., and Garceau, G. J.: Cerebral Spastic Paralysis: Obstetric History of One Hundred and Eighty-Five Cases, J. A. M. A. **116**:374-377 (Feb. 1) 1941.

383. Boorstein, S. W.: Cerebral Palsy Child, Arch. Pediat. **58**:578-596 (Sept.) 1941.

384. Brander, T.: Heredity of Congenital Spastic Hemiplegias, Acta pædiat. (supp. 1) **28**:114-122, 1940.

385. Haldane, J. B. S.: Partial Sex-Linkage of Recessive Spastic Paraplegia, J. Genetics **41**:141-147 (Jan.) 1941.

386. Jakob, C., and Scaravelli, A.: Idiocy, Deaf-mutism and Familial Spastic Quadriplegia in Seven Brothers and Sister, Rev. neurol. de Buenos Aires **5**:283-299 (Oct.-Dec.) 1940.

387. Phelps, W. M.: Differential Characteristics of Spasticity and Athetosis in Relation to Therapeutic Measures, New York State J. Med. **41**:1827-1831 (Sept. 15) 1941; Rehabilitation of Cerebral Palsy, South. M. J. **34**:770-776 (July) 1941; Factors Influencing Treatment of Cerebral Palsy, Physiotherapy Rev. **31**:136-138 (May-June) 1941; Correlation of Physical Therapy and Occupational Therapy in Cerebral Palsy, Arch. Phys. Therapy **22**:587-590 (Oct.) 1941.

Brachial Plexus Paralysis.—Ruhlin [388] presents a clinical study of obstetric paralysis and its relation to birth injury of the brachial plexus or the muscular, ligamentous and capsular apparatus around the shoulder joint. He feels that the disability is a common one; that the treatment is well standardized, and that gratifying results can be obtained in most cases. Finochietto and Dickmann [389] describe the traumatic lesions in the brachial plexus in adults and the technic of surgical treatment for them. Götze [390] describes lesions which have been found in peripheral nerve injuries of the brachial plexus. Kolodny [391] and Greiner [392] describe the causation of obstetric injuries and traction paralysis of the brachial plexus. Putti [393] describes the similarity between obstetric and poliomyelitis syndromes of the upper extremity and the surgical therapy to be used for some of these types. Lance [394] describes the so-called obstetric paralysis of the upper and lower extremities, which is not a brachial palsy in all cases but which may be a more generalized injury of the cord.

Tabetic Arthropathies.—Sashin [395] describes early tabetic arthropathy of the metatarsophalangeal joint of the great toe. He concludes that arthropathy is often the first sign of a tabetic process and that pain may definitely be present on motion in the early stages. Negative results of serologic tests do not rule out tabetic arthropathy. The earliest signs may be seen by roentgen examination. The author concludes that early diagnosis is most important in order that the joint may be protected and the development of an unstable and markedly deformed articulation prevented. Pomeranz and Rothberg [396] review 58 cases of tabetic arthropathy. The largest number of cases occurred

388. Ruhlin, C. W.: Clinical Study of Obstetric Paralysis, J. Maine M. A. **32**:205-208 (Sept.) 1941.

389. Finochietto, R., and Dickmann, G. H.: Traumatic Lesions of the Brachial Plexus in Adults: Technic of Surgical Therapy, Arch. argent. de neurol. **23**: 30-43 (July-Dec.) 1940.

390. Götze, W.: Lesions of the Brachial Plexus in Peripheral Nerve Injuries, Arch. f. Psychiat. **112**:469-473, 1940.

391. Kolodny, A.: Traction Paralysis of Brachial Plexus, Am. J. Surg. **51**: 620-629 (March) 1941.

392. Greiner, K.: Hemiplegia in Infant Due to Obstetric Trauma: Case, Kinderärztl. Praxis **11**:378-380 (Dec.) 1940.

393. Putti, V.: Obstetric and Poliomyelitic Paralytic Syndromes of Upper Extremity: Surgical Therapy with Note on Physiopathology of Rotation of Forearm, Chir. d. org. di movimento **26**:215-229 (Nov.) 1940.

394. Lance: So-Called Obstetric Paralysis of Upper and Lower Extremities: Case, Bull. Soc. de pédiat. de Paris **37**:512-513, 1940.

395. Sashin, D.: Early Tabetic Arthropathy of Metatarsophalangeal Joint of Big Toe, Bull Hosp. Joint Dis. **2**:105-110 (July) 1941.

396. Pomeranz, M. M., and Rothberg, A. S.: Review of Fifty-Eight Cases of Tabetic Arthropathy, Am. J. Syph., Gonor. & Ven. Dis. **25**:103-119 (Jan) 1941.

in the fifth and sixth decades of life in white male patients. The knee joint was affected in many cases, and there was multiple involvement in 19 cases. The authors also conclude that roentgen examination provides the most reliable diagnostic aid and that serologic tests may not always be positive. Pain is found to be present early in cases of arthropathy. The authors do not feel that fusion or stabilization operations are advisable in view of the end results which they have seen.

Meralgia Paraesthetica.—Lee [397] describes meralgia paraesthetica as a compression of and tension on the lateral femoral cutaneous nerve as it passes under the inguinal ligament. He concludes that this is the cause since in instances in which neurolysis was performed there resulted a progressively favorable increase in the sensation of the skin. He describes the operative treatment for the condition in which the nerve is relocated in a slot in the ileum. In this way normal sensation can be restored to the skin. King [398] describes the treatment of meralgia paraesthetica by resection of the segment of the femoral cutaneous nerve when the condition has been resistant to conservative therapy. He states that a diagnostic aid is the injection of procaine hydrochloride into the nerve trunk in the upper part of the thigh with relief of pain. A method of treating the condition is the injection of absolute alcohol into the cut ends of the nerve after section to prevent the formation of a neuroma. The author feels that in many cases relief may be obtained by conservative treatment rather than by operation and that conservative treatment should be tried first in all cases.

Myasthenia Gravis, Dystrophia Myatonica, Progressive Muscular Dystrophy and Other Conditions.—An article by Blalock, Harvey, Ford and Lilienthal [399] describes the treatment of myasthenia gravis by removal of the thymus gland. This article is in the form of a preliminary report on the effects of the removal of the thymus on the course of myasthenia gravis. It is felt that the results are encouraging and that these suggest that the thymus is concerned with the genesis of myasthenia gravis. They also suggest that the thymus is a gland with an internal secretion and that it may have a definite function. Harvey and Masland [400] have described the muscle contractions which charac-

397. Lee, F. C.: Osteoplastic Neurolysis Operation for Cure of Meralgia Paraesthetica, Ann. Surg. **113**:85-94 (Jan.) 1941.

398. King, B. B.: Meralgia Paraesthetica: Report of Five Cases, Am. J. Surg. **52**:364-368 (May) 1941.

399. Blalock, A.; Harvey, A. M.; Ford, F. R., and Lilienthal, J. L. J.: Treatment of Myasthenia Gravis by Removal of Thymus Gland: Preliminary Report, J. A. M. A. **117**:1529-1533 (Nov. 1) 1941.

400. Harvey, A. M., and Masland, R. L.: Electromyogram in Myasthenia Gravis, Bull. Johns Hopkins Hosp. **69**:1-13 (July) 1941.

teristically appear in the electromyogram in cases of myasthenia gravis. Boman [401] describes thymus changes seen in cases of myasthenia gravis.

Maybarduk and Levine [402] describe the atrophy seen in the bones and associated with progressive muscular dystrophy. They offer evidence that concentric osseous atrophy is a primary feature and is not secondary to disuse. They suggest that an endocrine disorder or a disturbance of the vegetative nervous system may be the source of these changes. Epstein and Abramson [403] also report interesting roentgen studies of patients with progressive muscular dystrophy which confirm some of the findings of Maybarduk and Levine. Lewis, Ravin and Lewis [404] discuss the excretion of creatine and creatinine and the effect of glycine administratiton on muscular dystrophy. They state that while the evidence is not sufficient for drawing complete conclusions it seems to augment the evidence that slight to moderate creatinuria which may be observed in cases of dystrophia myotonica is neither as constant nor as striking a finding as in cases of progressive muscular dystrophy and that the condition is less strongly affected by the administration of glycine than in cases of the latter disease. Milhorat,[405] in discussing the hereditary factors in the causation of muscular dystrophies, states that since the disease is associated with defective metabolism of creatine and creatinine it is possible that the factors causing creatinuria in childhood and infancy might be of importance in determining the early extensive distribution and rapid clinical progression of the process when the disease develops in the first decade of life.

Branch [406] divides pseudohypertrophic muscular dystrophy into the infantile and juvenile types. The infantile type shows the muscle to have a pale water-logged appearance with a degeneration of the individual fibers and profuse fibrous tissue between. The juvenile type presents more nearly normal muscle fibers, but there is an infiltration of fat between the fibers and there are fewer individual muscle fibers. A new regimen of treatment is described which includes the following measures: 1. Estrogenic substances are given to influence favorably the creatine-creatinine utilization and excretion. 2. Choline is given to

401. Boman, K.: Thymus Changes in Myasthenia Gravis, Nord. med. (Hygiea) **10**:1625-1634 (May 24) 1941.

402. Maybarduk, P. K., and Levine, M.: Osseous Atrophy Associated with Progressive Muscular Dystrophy, Am. J. Dis. Child. **61**:565-576 (March) 1941.

403. Epstein, B. S., and Abramson, J. L.: Roentgenologic Changes in Bones in Cases of Pseudohypertrophic Muscular Dystrophy, Arch. Neurol. & Psychiat. **46**:868-876 (Nov.) 1941.

404. Lewis, R. C., Jr.; Ravin, A., and Lewis, R. C.: Studies in Dystrophia Myotonica: Creatine and Creatinine Excretion, J. Lab. & Clin. Med. **26**:990-995 (March) 1941.

405. Milhorat, A. T.: Hereditary Factors in Muscular Dystrophies and Other Considerations, Tr. Am. Neurol. A. **66**:120-122, 1940.

406. Branch, H. E.: Progressive Pseudohypertrophic Muscular Dystrophy: New Regime of Treatment, J. Michigan M. Soc. **40**:814-822 (Oct.) 1941.

influence the metabolism and the deposition of fat. 3. Cow's or goat's milk is given to increase the magnesium content of the muscle. 4. An extract of the anterior lobe of the pituitary gland is given to hasten the growth of the patient to maturity.

The results of the treatment of 6 patients show that in 3 on the full regimen there was a marked increase in muscular power; in 2 there was definite improvement, and in 1 there was improvement until bilateral otitis media developed. These results are considered by the author to be encouraging.

Hauptmann and Thannhauser [407] report an apparently new hereditary familial disease in an article on muscular shortening and dystrophy. This condition affects only the muscular system and is not markedly progressive. It occurred in a family of French Canadians and was characterized by a short webbed neck with a normal roentgenogram of the cervical portion of the spine. There was also some evidence of shortening and weakening in many of the muscles. There were some features of progressive muscular dystrophy present.

Paralysis, Traumatic or Occupational.—Roger and Schachter [408] discuss peroneal and sciatic paralysis after gluteal injections of bismuth and present a case of paralysis of the external popliteal branch of the sciatic nerve. Guillain, Bourguignon and Corre [409] describe ulnar paralysis in bicyclers and report 4 cases. Ransohoff [410] describes peroneal paralysis caused by a cyst of the lateral meniscus of the knee joint. Hogan [411] reports multiple neuritis as a serum reaction with a discussion of 2 cases. He points out that this distinct clinical entity is a complication which may follow the use of serum therapy and should be more widely recognized. He states that it is important to know that it has a favorable prognosis.

Vitamin Therapy for Neuromuscular Disorders.—DeJong [412] writes concerning vitamin E in the treatment of amyotrophic lateral sclerosis.

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407. Hauptmann, A., and Thannhauser, S. J.: Muscular Shortening and Dystrophy: Heredofamilial Disease, Arch. Neurol. & Psychiat. **46**:654-664 (Oct.) 1941.

408. Roger, H.; Schachter, M., and Fournier, A.: Sciaticas After Intragluteal Injections of Bismuth: Case of Paralysis of External Popliteal Branch of Sciatic Nerve, Medicina, Madrid **9**:172-178 (March) 1941.

409. Guillain, G.; Bourguignon, G., and Corre: Ulnar Paralysis of Cyclists: Report of Four Cases, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:489-492 (Sept. 24) 1940.

410. Ransohoff, N. S.: Cyst of Lateral Meniscus Causing Peroneal Nerve Palsy, Bull. Hosp. Joint Dis. **2**:69-71 (April) 1941.

411. Hogan, B. W.: Neuritis as Serum Reaction: Report of Two Cases, U. S. Nav. M. Bull. **39**:403-408 (July) 1941.

412. DeJong, R. N.: Vitamin E and Alpha-Tocopherol Therapy of Neuromuscular and Muscular Disorders, Arch. Neurol. & Psychiat. **46**:1068-1075 (Dec.) 1941.

He states that no outstanding clinical response can be demonstrated either in cases of amyotrophic lateral sclerosis or in cases of progressive spinal muscular atrophy with bulbar palsy. The only changes of significance are a slight decrease in the fibrillary tremors, a feeling of well-being and a slight gain in weight in some patients. There may also be a subjective increase in muscular strength in the early course of the therapy. The author feels that the progress of the disease may have been retarded or arrested in certain instances but that this is purely speculative since the pathologic process advances with varying speed in different people. Large doses of vitamin E, or alpha tocopherol, have no advantage over smaller doses. Eaton, Woltman and Butt [413] write of vitamin E and vitamin B_6 in the treatment of neuromuscular diseases. They found no conclusive evidence that vitamin E alone or in combination with vitamin B or other vitamins is of any benefit in the treatment of amyotrophic lateral sclerosis, progressive muscular atrophy or progressive muscular dystrophy. Meller [414] likewise has evaluated the use of vitamin E in the treatment of multiple sclerosis and progressive muscular atrophy and concludes that in 12 cases of multiple sclerosis no response to intensive therapy with vitamin E was found. However, in 14 cases of varying types of progressive muscular atrophy 3 patients apparently recovered; 7 showed definite improvement, and 4 failed to respond. The author points out that large doses over a long period of time are necessary; he observed no toxic symptoms attributable to the medication. Telford [415] describes the degeneration and the loss of nerve endings in the degenerated skeletal muscles of young vitamin E–deficient rats. Many of these writers are unable to explain the startling results seen in rats and the lack of any specific response to treatment with vitamin E in human beings. Hanisch [416] describes the successful use of a vitamin B complex preparation made from yeast and wheat germ in the treatment of myotonia congenita. In an extensive article on the nature of certain diseases of the voluntary muscles Gammon, Harvey and Masland [417] describe in great detail the relation of the various muscular diseases to the present use of biochemicals.

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413. Eaton, L. M.; Woltman, H. W., and Butt, H. R.: Vitamins E and B in the Treatment of Neuromuscular Diseases, Proc. Staff Meet., Mayo Clin. **16:** 523-527 (Aug. 13) 1941.

414. Meller, R. L.: Evaluation of Vitamin E in Treatment of Multiple Sclerosis and Progressive Muscular Atrophies, Journal-Lancet **61:**471-478 (Dec.) 1941.

415. Telford, I. R.: Loss of Nerve Endings in Degenerated Skeletal Muscles of Young Vitamin E Deficient Rats, Anat. Rec. **81:**171-181 (Oct. 25) 1941.

416. Hanisch, P.: Successful Therapy of Oppenheim's Myatonia with Eugenozym (Vitamin B Preparation), München. med. Wchnschr. **88:**304-305 (March 14) 1941.

417. Gammon, G. D.; Harvey, A. M., and Masland, R. L.: On Nature of Certain Diseases of the Voluntary Muscles, Biol. Symposia **3:**291-330, 1941.

Oldberg [418] describes the different types of pain arising from various types of nerve lesions. First he presents a case of pain arising from an extramedullary intradural spinal tumor, then a second case of tabetic radiculitis, a third of postherpetic neuritis, a fourth of alcoholic-avitaminotic peripheral neuritis, a fifth of peripheral neurofibroma, a sixth of neuritis resulting from focal infection, a seventh of neuritis due to cervical rib and an eighth of pain caused by a protruded intervertebral disk.

These are fairly typical examples of specific types of pain, and the paper is an interestinng and important description of the differences between these various syndromes.

Surgical Technics.—Finochietto and Dickmann [419] describe the technic for exposure in the lower half of the arm and the elbow of the radial nerve. This is a posterior route and appears to be a satisfactory exposure. Malan [420] describes the grafting of spinal cord or nerve in the process of repair for loss of peripheral nerve substance with satisfactory results.

XI. TUMORS OF BONE

Experimental Work.—To produce tumors experimentally Turner [421] implanted bakelite disks in 13 rats. In 4 of 9 rats living over twenty months fibrosarcomatous tumors developed about the disks. The bakelite disks probably served as another carcinogenic agent of low potency, and the development of tumor tissue may have been entirely due to chronic irritation.

Franseen, Aub and Simpson,[422] implanting methylchloranthine crystals resulting from the evaporation of colloidal thorium dioxide and radon seeds near the upper tibial epiphysis in rats, failed to produce osteogenic sarcomas but did produce fibrosarcomas, probably extraosseous with origin in muscle.

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418. Oldberg, E.: Pain Arising from Lesions of Nerves and Spinal Cord: Differential Diagnosis and Treatment, M. Clin. North America **25**:55-62 (Jan.) 1941.

419. Finochietto, R., and Dickmann, G. H.: Technic for Exposure of Radial Nerve in Lower Half of Arm and Elbow by Posterior Route, Rev. de cir. de Buenos Aires **19**:10-17 (Jan.) 1940.

420. Malan, R.: Results of Grafting Spinal Cord or Nerve in Process of Repair of Loss of Peripheral Nerve Substance: Experimental Study, Arch. per le sc. med. **70**:587-605 (Dec.) 1940.

421. Turner, F. C.: Sarcomas at Sites of Subcutaneously Implanted Disks in Rats, J. Nat. Cancer Inst. **2**:81-83 (Aug.) 1941.

422. Franseen, C. C.; Aub, J. C., and Simpson, C. L.: Experimental Production of Fibrosarcomas of Bone, Cancer Research **1**:393-396 (May) 1941.

In the field of experimental therapy Stark [423] has studied the effects of various ultraviolet light wavelengths on living sarcoma cells. She had noted that certain stages of spermatogenesis reacted to λ 2,750 wavelength. Following her work on the rat sarcoma no. 39 from the Crocker Institute, she proves that there is no relation between the absorption and the lethal effect of light and that wavelengths shorter than λ 2,573 are destructive and lethal in three seconds at λ 2,300. She feels that the lethal effects of shorter wavelengths can probably be utilized in surface irradiation or that they can be generated within the cells by impregnation with some substance which under the action of still shorter wavelengths, such as roentgen rays, will cause the substance to emit the shorter ultraviolet waves. Such experiments have been started. [ED. NOTE: This work is interesting but rather technical and probably could be more appreciated if a similar series of experiments were run with roentgen rays of varying lengths.]

Blood chemistry with the determination of serum and tissue phosphatase still presents diagnostic aid of some value, but only when positive reactions are obtained. Woodard and Higinbotham [424] have determined a normal alkaline serum phosphatase content of 1.5 to 5 units for adults and 5 to 13 units for children. Their standard for the acid serum phosphatase is usually less than 5 per cent of the alkaline value. They conclude that benign tumors of bone produce much phosphatase which does not enter the circulation and some which does enter. They have shown that the phosphatase mechanism of tumors is inactivated by roentgen therapy when the dose is 4,000 r or greater. They have demonstrated that the giving of radioactive phosphorus by mouth will localize portions of the tumor containing the most phosphatase, and they feel that the changes in the phosphatase afford definite indication of the effect of roentgen therapy. These findings are of value only in those cases in which the serum phosphatase value is above normal.

Herger and Sauer [425] have studied the relation of the serum acid phosphatase value to the presence of metastasis from carcinoma of the prostate. They conclude that determination of the serum acid phos-

423. Stark, M. B.: Effect of Various Ultraviolet Light Wave Lengths upon Living Sarcoma Cells, New York M. Coll. & Flower Hosp. Bull. **3**:358-371 (Dec.) 1940.

424. Woodard, H. Q., and Higinbotham, N. L.: Serum and Tissue Phosphatase Determinations as Aid in Evaluating Radiation Therapy, J. A. M. A. **116**:1621-1627 (April 12) 1941.

425. Herger, C. C., and Sauer, H. R.: Relationship of Serum Acid Phosphatase Determination to Presence of Metastases from Carcinoma of Prostate, J. Urol. **46**:286-302 (Aug.) 1941.

phatase is a valuable adjunct in the diagnosis of bone metastasis. If the determination gives a value of 4 to 6 units, metastasis is possible; if the value is over 6 units, metastasis is probable. The rapid progressive elevation of the acid serum phosphatase offers a bad prognostic sign.

Classification.—In 1941 the literature on bone tumors continued to contain various critical viewpoints on the classification of osteogenic tumors. Jacobson [426] in a critique on interrelationships of osteogenic tumors states that the present attitude is not logical in the consideration of the interrelationships of the tumors of the skeletal tissues. In this excellent article he outlines fourteen groups of bone tumors, giving somewhat in a visual way the tissues of origin from which are developed the benign and malignant bone tumors. The classification is as follows:

1. Periosteal fibroma. This is theoretically possible.
2. Periosteal fibrosarcoma. This is theoretically possible.
3. Central fibroma. This is presumably derived from the connective tissue of marrow.
4. Medullary fibrosarcoma. This probably occurs more frequently than is recognized; possibly it is often mistaken for osteolytic osteogenic sarcoma.
5. Lipoma and liposarcoma. The first is impossible to recognize; the second has been described.
6. Enchondroma. This probably is caused by failure of absorption of part of the cartilage growth plate.
7. Chondrosarcoma. The author believes that in all cases this tumor is derived from preexisting nonmalignant cartilage cells.
8. Ecchondrosis. This is presumably derived from perichondrium.
9. Cartilaginous exostosis. This is periosteal dysplasia in hereditary form. The single form may be traumatic. The author gives a long discussion.
10. Osteoma. This is the same as cartilaginous exostosis in membranous bones.
11. Osteoid osteoma. This is an endosteal neoplasm.
12. Osteogenic sarcoma. The chondroplastic type is rare and variable.
13. Giant cell tumor. The author feels that in all cases in which it is endosteal in origin it is related to the two classes just mentioned. It develops from osteoid osteoma through giant cell tumor to osteogenic sarcoma. Its development is dependent on the metabolic activity of the region in which it arises; this is low in the diaphysis and the epiphysis and high in the metaphysis. The more malignant developments are all composed of the same elements, viz., spindle cells, osteoblasts, osteoid, bone and giant cells.
14. Heterotopic bone tumors. These have the same potentialities as osteoplastic and chondroplastic tumors.

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426. Jacobson, S. A.: Critique on Interrelationships of Osteogenic Tumors, Am. J. Cancer **40**:375-402 (Nov.) 1940.

Roentgen Studies.—In a study of growth in 200 children Sontag and Pyle [427] have made serial roentgenograms started at birth and repeated each three to six months up to 18 years of age. In this mass of roentgen material they have observed cystlike areas in the distal metaphyses of the femurs of children between the ages of 2 and 9 years. The average duration is twenty-nine months. These cysts are asymptomatic and disappear spontaneously. They are interpreted as the result of local removal of bone salts or as due to the inclusion of small groups of cartilage cells; on the other hand, they may be of the same pathologic nature as solitary cysts in origin, only they do not progress with their osteoclastic tendency. No biopsies have been done. This is altogether a clinical and roentgen study. [ED. NOTE: The authors should have excellent material for studies of bone growth.]

In a discussion on roentgenography in the diagnosis of bone tumors, Sutherland [428] presents two fundamental principles: First, with benign tumors of bone the continuity of the contour of the bone is retained. Second, with malignant tumors of bone there is dissolution of the contour shadow, and this applies to the soft tissue shadows as well. To these fundamentals there are three exceptions, namely, tumors of soft tissue, periosteal fibrosarcoma and Ewing's tumor. This is an elementary discussion of the roentgen differentiation of the various types of bone tumors and is of value particularly from the teaching standpoint.

Benign Tumors of Bone.—In the literature of the past year there are 2 additional case reports of osteoid osteoma, which has been previously described by Jaffe.

A tumor in the upper part of the tibia with a differential diagnosis of osteomyelitis, sclerosing osteitis of Garré or an osteoid osteoma is described as a Cabot case.[429] Exploration of this tumor with tissue study and negative cultures confirmed the diagnosis.

The second case was reported by Kleinberg.[430] The patient was a 24 year old man with a painful tumor of the femur in the midshaft in the cortical bone. This tumor existed for four years. At the end of two years the tumor was biopsied, and the diagnosis of osteomyelitis

427. Sontag, L. W., and Pyle, S. I.: Appearance and Nature of Cyst-Like Areas in Distal Metaphyses of Children, Am. J. Roentgenol. **46**:185-188 (Aug.) 1941.

428. Sutherland, C. G.: Roentgenography in Diagnosis of Tumors of the Bone, M. Clin. North America **25**:1041-1065 (July) 1941.

429. Osteoid Osteoma of the Tibia, Cabot Case 27492, New England J. Med. **225**:920-922 (Dec. 4) 1941.

430. Kleinberg, S.: Osteoid Osteoma of Femur, Am. J. Surg. **53**:168-171 (July) 1941.

was made. Two years later a second exploration was done; the tumor was removed and diagnosed pathologically by Jaffe as an osteoid osteoma.

The literature of the past year on chondroma consists chiefly of individual case reports. Pearce and Collins [431] report a tumor in the shaft of the ulna showing rapid growth. On microscopic examination it was not definitely malignant, though the clinical course was definitely strongly suggestive. [ED. NOTE: One of us (R. D. S.) interprets this tumor as probably an enchondroma activated by trauma.]

An interesting case is reported by Carter and Heitzman.[432] The diagnosis was Ollier's dyschondroplasia with multiple chrondromas of all bones of one lower extremity and the pelvis. This was treated by disarticulation at the hip joint. There has been no evidence of malignant growth in these sections. This case is well reported with splendid photographs and photomicrographs.

Mayer [433] reports a case in which excision of chondroma of the ribs was followed three years later by recurrence which showed on clinical and microscopic examination the signs typical of chondrosarcoma. The tumor was treated by wide excision of the anterior chest wall including the pleura and an immediate transplantation of fascia lata. There had been no recurrence of the tumor five years from the time of the second excision.

Giant Cell Tumor.—In a study of giant cell tumor Lichtenstein and Jaffe [434] express the firm opinion that the diagnosis of giant cell tumor is made too frequently, and they regard the numerous variants as being in reality incorrect diagnoses. In their opinion the giant cell tumor of bone is a neoplasm of definite kind, arising apparently from the undifferentiated supporting tissue of the marrow and clearly delimitable on the basis of the cytologic details. Essentially it is composed of more or less vascularized network of spindle-shaped or ovoid stromal cells in multinuclear giant cells in certain particular proportions and arrangements. The tumor shows but little collagenous differentiation of its stroma and almost no evidence of ossification. Stromal cells are really the more significant component.

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431. Pearce, T. V., and Collins, D. H.: Cartilaginous Tumor of Shaft of Ulna, Brit. J. Surg. **28**:432-435 (Jan.) 1941.

432. Carter, R. M., and Heitzman, H.: Chondroma of Bone, Tr. West. S. A. (1939) **49**:307-322, 1940.

433. Mayer, L.: Chondrosarcoma of Rib: Five Year Cure After Resection, J. Mt. Sinai Hosp. **7**:467-470 (Jan.-Feb.) 1941.

434. Lichtenstein, L., and Jaffe, H. L.: Giant Cell Tumor of the Bone, Bull. Hosp. Joint Dis. **2**:95-104 (July) 1941.

On the basis of the stromal cell detail the authors have classified the giant cell tumor into the three grades as follows:

Grade 1: This is the least aggressive. Stromal cells, though abundant, are not compacted and do not exhibit any appreciable atypism. About one half of any representative series of giant cell tumors of bone will be of this grade. The prognosis is relatively favorable, but recurrence may occur.

Grade 2: Cytologically a tumor of this grade manifests a compact cellular stroma showing definite evidences of atypism. It tends strongly toward recurrence and may eventually undergo malignant transformation.

Grade 3: In this grade are represented the small group of tumors which possess a sarcomatous type of stroma, are frankly malignant and metastasize with abundant compacted stromal cells appearing in whorled arrangement and uniformly showing signs of atypism.

The authors discuss further the diagnosis from the standpoint of the roentgen findings and urge an adequate yet conservatively planned biopsy with frozen section studies.

Between the aforementioned authors and Leucutia, Witmer and Belanger [435] there is good ground for profitable discussion. These three authors report 33 cases of giant cell tumor, in 18 of which treatment was by roentgen therapy alone. The 18 patients showed good results, and the authors conclude that roentgen therapy is the treatment of choice in the treatment of all giant cell tumors and of all pathologic growths related to cystic conditions in bone. Adequate biopsies were not sufficiently frequent in this series. Some of these tumors were in the diaphyses of long bones, while others were in the metaphyses but did not involve the epiphyses. The authors apparently are of the opinion that the giant cell tumor is a product of inflammation and repair rather than a true blastoma.

A five year cure of a benign giant cell tumor with irradiation alone is reported by Edieken.[436] The original roentgenogram shows more metaphysial change than epiphysial, and in other elements it is not typical. However, the aspiration biopsy revealed fairly typical characteristics. A total of 2,223 r units was given in two series over a period of four months.

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435. Leucutia, T.; Witmer, E. R., and Belanger, G.: Late Results in Benign Giant Cell Tumors of Bone Obtained by Radiation Therapy, Radiology **37:** 1-17 (July) 1941.

436. Edieken, L.: Benign Giant Cell Tumor: Five Year Cure, Am. J. Roentgenol. **44:**884-886 (Dec.) 1940.

The surgical treatment of giant cell tumor is discussed by Inclán.[437] His series of tumors is reported to demonstrate various surgical procedures. In treating those giant cell tumors seen early and without previous interference Inclán follows the usual procedure of curettage. When there is recurrence of the tumor and also when the tumor is of the aggressive type, mass resection is urged. In those cases in which the tumor is seen too late or in which as a result of previous interference there is secondary infection or in which there is no doubt regarding the malignancy of the tumor, amputation is the method of choice.

In his thorough and characteristic manner Meyerding [438] discusses the benign and malignant giant cell tumors of bone from the standpoint of the diagnosis and the result of treatment. He recognizes with Lichtenstein and Jaffe [434] that a confusion exists in regard to this group of tumors. He regards part of the confusion as due to the early use of the term "giant cell sarcoma." He recognizes much similarity of tissue in cases of giant cell tumor, osteitis fibrosa cystica and hyperparathyroid osteodystrophy. These tumors are regarded as radiosensitive and possessing a low degree of malignancy. In this paper there is presented an analysis of 124 patients of whom 19 per cent presented signs of malignancy in giant cell tumors. He recognizes that malignant changes may develop in apparently benign tumors and that an accurate diagnosis can hardly be made without careful microscopic study. The treatment recommended is surgical removal when possible. There is demonstrated increasing value in adequate irradiation alone or as an adjunct to surgical procedures postoperatively. The five year survival rate in this series of benign giant cell tumors is 97 per cent. In those giant cell tumors showing malignant tendencies the five year survival rate is 65 per cent. Meyerding properly contends that this survival rate will be higher when the patients are seen early by those surgeons who have had extensive experience in dealing with this particular type of tumor of bone.

An unusual multiple hemangioma of bone, probably congenital in origin, is described by Pierson, Farber and Howard.[439] At the time of writing the patient was 21 years of age; his condition was diagnosed when he was 16 years of age as hyperparathyroidism. The diagnosis was based primarily on the roentgen demonstration of multiple cystic areas in bone, particularly in the skull and the pelvis, but none of these

437. Inclán, A.: Surgical Treatment of Giant Cell Tumors, Cir. ortop. y traumatol., Havana **8**:63-87 (July-Sept.) 1940.

438. Meyerding, H. W.: Benign and Malignant Giant Cell Tumors of the Bone: Diagnosis and Result of Treatment, J. A. M. A. **117**:1849-1855 (Nov. 29) 1941.

439. Pierson, J. W.; Farber, G., and Howard, J. E.: Multiple Hemangiomas of Bone, Probably Congenital, J. A. M. A. **116**:2145 (May 10) 1941.

lesions were below the elbows or the knees. An early biopsy of a lesion in the rib was interpreted as indicating osteitis fibrosa cystica. All other laboratory findings, including detailed blood studies, were essentially normal. On a later biopsy of a lesion in the rib, a diagnosis of cavernous hemangioma was made. To the time of writing these lesions were apparently not progressive, and the patient had remained in excellent general health. The writers point out the possibility of this condition existing when the clinical pictures are not definite in cases of hyperparathyroidism, osteitis fibrosa disseminata or xanthomatosis.

Glomus Tumor.—The glomus tumor does not belong in the class of hemangioma, although there are vascular elements that relate it to hemangioma to a certain degree. This tumor is of interest from the standpoint of both diagnosis and treatment.

An interesting description of the clinical picture and physiologic characteristics of glomus tumor in the fingers and the toes is written by Couch.[440] Apparently the glomera have to do with heat regulation and bear a close relation to the sympathetic system. Evidently there is a shunt of blood from the arterioles to the venules when the hand is exposed to cold. The pain in the tumor is similar to the intense pain on exposure to cold. The outstanding symptoms are tumor with severe pain, exquisite tenderness, warmth and pinkness with perspiration and a moderate Horner's syndrome.

Another case of glomus tumor in the finger is reported by Rypins,[441] who presents a good description with sketches of the glomus tumor and with roentgenograms which show cleancut destruction of the cortex of the distal phalanx.

Multiple glomus tumors with four in one finger tip are reported by Plewes.[442] These were progressive for several months and showed improvement following excision.

Glomus tumors with intramuscular lipoma were reported by Hoffmann and Ghormley.[443] One patient had an injury to the knee in 1916, followed by menisectomy in 1918 and excision of the scar in 1928 without relief. There was severe pain localized on the medial aspect of the knee.

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440. Couch, J. H.: Glomus Tumors: Clinical Picture and Physiology, Canad. M. A. J. **44**:356-357 (April) 1941.

441. Rypins, E. L.: Roentgenologic Aspects of Subungual Glomus Tumor, Am. J. Roentgenol. **46**:667-672 (Nov.) 1941.

442. Plewes, B.: Multiple Glomus Tumors: Four in One Finger Tip, Canad. M. A. J. **44**:364-365 (April) 1941.

443. Hoffmann, H. O. E., and Ghormley, R. K.: Glomus Tumor and Intramuscular Lipoma: Two Cases, Proc. Staff Meet., Mayo Clin. **16**:13-16 (Jan. 2) 1941.

On recent exploration the authors found in the synovium a glomus tumor the size of a bean. This was excised, and the patient was completely relieved.

Primary Malignant Tumors of Bone.—The outstanding publication in the study of these malignant tumors has been made by Meyerding [444] and Meyerding and Valls.[445] This is an analytic study of 424 primary malignant tumors of bone observed at the Mayo Clinic, Rochester, Minn. In these cases biopsy was made whenever possible, and consideration was given to Broders' method of gradation in the malignancy of these tumors. The various groups of malignant tumors in this statistical study are as follows:

1. Osteogenic sarcoma including chondrosarcoma accounted for 50.9 per cent of the malignant bone tumors. Sixty-seven and six tenths per cent of the patients were male. The average age was 29.3 years, and over 50 per cent were less than 30 years of age. The average duration of symptoms was ten months, and the history of trauma was given in 44 per cent of the cases. These tumors occurred in the femur in 37.7 per cent of the cases. The treatment of choice was operation, this method giving a five year survival rate of 23.4 per cent. There were no five year survivals among the patients treated otherwise.

2. Fibrosarcoma was the tumor in 38 per cent of the cases. In this group 60.5 per cent of the patients were male. Also 60.5 per cent were less than 30 years of age. The femur was most frequently involved in 34.3 per cent of the cases. A history of trauma was obtained in 39.5 per cent of the cases. With amputation there was a five year survival rate of 40 per cent. In the group of patients treated by roentgen therapy there was a five year survival rate of only 16.7 per cent. In those treated by roentgen therapy there was recognized the lower grade of malignancy.

3. Ewing's tumor was the malignant growth of 114 patients, or 27 per cent. Of these 71.9 per cent were male, and 76 per cent were below 30 years of age. The femur was involved in 26.3 per cent and a history of trauma was elicited from 35.1 per cent. The five year survival rate after roentgen therapy alone was 37.5 per cent. After biopsy and roentgen therapy the five year survival rate was 20.5 per cent. After excision of the tumor with or without roentgen radiation, the survival rate was 16.7 per cent. Amputation alone or the combination of amputation with roentgen therapy or with Coley's toxin or with both showed a five year survival rate of 24.2 per cent.

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444. Meyerding, H. W.: Malignant Tumors of Bone, Proc. Staff Meet., Mayo Clin. **16**:70-71 (Jan. 29) 1941.

445. Meyerding, H. W., and Valls, J. E.: Primary Malignant Tumors, J. A. M. A. **117**:237-243 (July 26) 1941.

4. Multiple myeloma was present in 9.7 per cent of the cases in these series. Of these patients 75.6 per cent were male and 73.2 per cent were between the ages of 40 and 70 years. In 51.2 per cent of the cases there were multiple lesions. A history of trauma was given in 31.7 per cent. Only 1 patient, 3.6 per cent of this series, survived for more than five years.

5. Giant cell sarcoma, or the malignant giant cell sarcoma, was present in 1.6 per cent of the cases in this series; in 83.3 per cent the patients were under the age of 40. For this small group, the five year survival rate was 83.3 per cent.

From such an extensive study it is proper to quote verbatim the author's general impressions:

> It is obvious, from long experience, that roentgenologic treatment of tumors of bone is not a cure. Yet, such treatment has an important field of usefulness. Roentgen rays are invaluable in diagnosis, prognosis and treatment of certain types of tumors, especially Ewing tumors, and furnishes the earliest knowledge of the presence of pulmonary metastasis. The possibilities of irradiation, we believe, have not been exhausted, and with the passage of time its application will be improved and its therapeutic value increased.
>
> We are firmly convinced that surgical operation offers the best method of treatment for the majority of primary malignant tumors of bone.
>
> We urge surgeons, roentgenologists and pathologists to cooperate, for only through their combined efforts will diagnosis, prognosis and therapeutic measures be improved. Equally important is education of the practitioner of internal medicine in recognizing the presence of these malignant tumors and in seeking immediate consultation with those experienced and qualified to give advice. Only through early diagnosis, efficient early treatment and careful follow-up investigation can more extremities and lives be saved than have been saved in the past.

Osteogenic Sarcoma.—A series of 160 cases of osteogenic sarcoma has been studied by Coley and Pool [446] from the standpoint of prognosis. The prospect of five year survivals is most favorable in patients between the ages of 20 and 40 years; it is least favorable in the first decade or after the fourth decade. Osteogenic sarcoma superimposed on Paget's disease gives an extremely bad prognosis. These conditions are found usually in the fifth, sixth and seventh decades of life. In general the five year survival rate for female patients was found to be 23 per cent; for male patients, 18 per cent. The more peripheral the lesion, the more favorable was found to be the outcome. Grouped according to the various gradations of malignancy, the patients with low grade lesions showed a 40 per cent five year survival rate; those with tumors of intermediate grade malignancy showed a 16 per cent survival rate, and those with

446. Coley, B. L. and Pool, J. L.: Factors Influencing Prognosis in Osteogenic Sarcoma, Ann. Surg. **112**:1114-1128 (Dec.) 1940.

growths of high grade malignancy, a 15 per cent survival rate. Of those patients on whom amputation was done 35 per cent survived five years when the amputation was done through the bone involved; 21 per cent survived when there was disarticulation at the joint above the involved bone, and 36 per cent showed a five year survival rate when amputation was done through the bone proximal to the bone which was affected. Roentgen therapy alone gave only a 9 per cent five year survival rate. Amputation with preoperative conservative surgical procedures or with preoperative roentgen therapy gave a five year survival rate of 32 per cent.

Apparently in this series of osteogenic sarcoma the therapeutic agents used had been narrowed down to roentgen therapy and operation. With the radical surgical attack showing the higher percentage of five year survivals, further elucidation of the time factor between the onset of the disease and the institution of radical operation would be of major interest as an element in prognosis.

In an analysis of 80 cases of osteogenic sarcoma Badgley and Batts [447] show that this is primarily a disease of young and especially of male patients, that trauma occurs in one third of the cases, that the average duration is thirteen months, that pain and swelling are the outstanding findings and that 50 per cent of these tumors occur about the knee region. Their treatment of choice is amputation, and the mortality rate for this series is 79 per cent with an average duration of forty-one months. Their five year survival rate is 19 per cent and their ten year survival rate is 5 per cent. One patient is described as surviving thirteen years after midthigh amputation and dying of pulmonary metastasis. These authors regard the prognosis more favorable for patients over 20 years of age and definitely less favorable for patients with a relatively short duration of signs or symptoms before coming for observation. The prognosis varies with the degree of differentiation of tumor tissue as an index of the grade of malignancy, and the prognosis becomes progressively better as the patient outlives his lesion after its surgical removal. The authors do not feel that biopsy carefully performed will increase the danger of dissemination of the tumor.

Another communication by Batts [448] shows a review of 27 cases of periosteal fibrosarcoma. These were taken from a series of 200 primary malignant growths in bone. The author's analysis shows that 78 per cent of the patients were under 40 years of age and that 63 per cent were

447. Badgley, C. E., and Batts, M., Jr.: Osteogenic Sarcoma: Analysis of Eighty Cases, Arch. Surg. **43**:541-550 (Oct.) 1941.

448. Batts, M., Jr.: Periosteal Fibrosarcoma, Arch. Surg. **42**:566-576 (March) 1941.

male. The average duration of symptoms was twenty months, pain being deep seated and swelling being firm and moderately tender. The superficial vessels were not commonly dilated, and the site of the lesions was near the ends of the long bones. The roentgen appearance was that of smooth bone with erosion under the tumor or a reactive thickening and roughening of the cortex. True bone formation was not present. Batts states that these tumors arise from the fibrous layer of periosteum, that they are similar to any other type of fibrosarcoma and that the osseous changes are altogether secondary. Treatment was by roentgen therapy, excision or amputation or a combination of these three methods. Improvement was noted from roentgen therapy, and in some cases the pulmonary metastases were cleared. This is contrary to the usual supposition that fibrosarcoma of bone is usually radioresistant. In this series there was a 40 per cent five year survival rate. Apparently the author feels that the grade of malignancy of the tumor as indicated by microscopic study is the major element in prognosis.

In an exhaustive discussion of roentgen considerations in the diagnosis and the treatment of primary malignant tumors of bone Howes and Schenck [449] report 40 cases and summarize the characteristics of each type of tumor. In their opinion the best treatment is a combination of roentgen therapy and operation. They present a classification which follows essentially the classification of the Committee of the Registry of Bone Sarcoma of the American College of Surgeons. The first three groups include the tumors arising from elements essential in the formation of bone:

I. Osteogenic series—sarcoma
   1. Medullary and subperiosteal
   2. Telangiectatic
   3. Sclerosing
   4. Periosteal
   5. Fibrosarcoma
      a. Medullary
      b. Periosteal
   6. Parosteal or capsular

II. Chondroma series
   1. Chondrosarcoma
   2. Myxosarcoma

III. Giant cell tumor series
   1. Malignant

449. Howes, W. E., and Schenck, S. G.: Roentgenologic Considerations in Diagnosis and Treatment of Primary Malignant Bone Tumors, Radiology **37:** 18-34 (July) 1941.

IV. Angioma series
  1. Angioendothelioma
  2. Diffuse endothelioma or Ewing's tumor
V. Myeloma series
  1. Plasma cell
  2. Myelocytoma
  3. Erythroblastoma
  4. Lymphocytoma
VI. Reticulum cell sarcoma
  1. Lymphosarcoma
VII. Liposarcoma

Central chondrosarcoma of the femur in a patient 6 years of age is reported by Kennedy.[450] This tumor was resected by curettage, cauterized with 50 per cent solution of zinc chloride and radiated postoperatively. This boy was in good general health with no evidence of local recurrence at the end of six years. The femur shows but 1 inch (2.5 cm.) shortening. This tumor is classified in the Registry of Bone Sarcoma as an osteogenic sarcoma, chondrosarcoma type, and the prognosis is good. In a discussion it is brought out that central chondroma occurs commonly in the bones of the hand, the feet and the spine, also in the ribs and rarely in the long bones. [ED. NOTE: Geschickter and Copeland report an incidence of only 5 in 2,000 cases. Apparently as a result of its rarity, this tumor is classed simply as chondrosarcoma in order to give it a pigeonhole. In view of the early onset of the tumor in the author's case with no evidence of recurrence after six years there seems to be room for argument as to whether this was simple chondroma or chondrosarcoma of low grade malignancy.]

Turner [451] reports simply the successful hindquarter amputation for chondrosarcoma of the ilium in a patient 49 years old. This man presented generalized osteitis deformans. The case is apparently presented from the standpoint of the technic rather than from the standpoint of the disease itself.

Myeloma.—Paul and Pohle [452] review 45 cases of myeloma from the literature and add 4 of their own. In some cases myeloma, solitary for a long period, eventually develops multiple lesions. In this series of

450. Kennedy, R. H.: Central Chondrosarcoma of Femur, Ann. Surg. **114**: 1106-1110 (Dec.) 1941.

451. Turner, G. G.: Hind-Quarter Amputation for Chondrosarcoma, Proc. Roy. Soc. Med. **34**: 562-563, (July) 1941.

452. Paul, L. W., and Pohle, E. A.: Solitary Myeloma of Bone: Review of Roentgenologic Features, with Report of Four Additional Cases, Radiology **35**: 651-666 (Dec.) 1940.

cases, 35 patients were male, and the average age was 48 years. The most frequent locations of the lesion are the spine, the pelvis and the proximal portion of the femur. Bence Jones proteinuria will be present in 20 per cent of the cases but usually only after the lesions become generalized. The roentgen characteristics may be either the osteolytic, very multicystic in appearance similar to the giant cell, or the osteolytic with trabeculations and with less tendency for expansion. In the spine the tumor tends to cross the intervertebral disk, but there is no proliferation of bone. The authors regard these tumors as radiosensitive. Their entire study tends to support the viewpoints that multiple myeloma is the result of metastasis from a primary focus and that there are varying grades of malignancy between the local benign form and the multiple, which may be highly malignant. In their opinion roentgen therapy is the most effective single agent; however, they do urge biopsy with excision of the tumor if this is solitary and surgically accessible. They feel that biopsy followed by roentgen treatment alone seems to offer the best prognosis. In this series 41 tumors were of the plasma cell type.

A questionable solitary myeloma of the spine with involvement of the cord is reported by Kamman.[453] The tumor was extradural; the bone involvement was not gross, but plasma cells were demonstrated in the neural arch. The case report is rather incomplete because there are no roentgenograms of the skull, the pelvis or the long bones.

Another case of plasma cell myeloma of the femur with three pathologic fractures over a period of twelve years and with a coexisting cystic lesion in a rib in which biopsy was not done is reported by Kirsch.[454] [ED. NOTE: For a long period this was clinically regarded as a giant cell tumor.]

Two cases of multiple myeloma are reported. The 1 reported by Perillo [455] represents something of a rarity on account of the early age of the patient, 25 years. There were associated no proteinuria, a normal serum protein, a high blood calcium and persistent hypertension without cardiorenal damage. The second case, reported as a Cabot case,[456] was one of diffuse plasma cell myeloma with elevated serum protein, phosphatase and spinal fluid protein. There was persistent anemia without definite roentgenographic change and no Bence Jones proteinuria. The diagnosis was made by sternal puncture and confirmed at autopsy.

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453. Kamman, G. R.: Solitary (?) Myeloma of Spine with Cord Involvement: Case Report, Minnesota Med. **24**:210-212 (March) 1941.

454. Kirsch, I. E.: Plasma-Cell Myeloma of Bone of Over Twelve Years' Duration, M. Bull. Vet. Admin. **18**:96-97 (July) 1941.

455. Perillo, J. A.: Multiple Myeloma: Report of Unusual Case, Radiology **36**:741-744 (June) 1941.

456. Diffuse Plasma Cell Myeloma, Cabot Case 27131, New England J. Med. **224**:559-564 (March 27) 1941.

Grossly allied with myeloma is the solitary plasmocytoma reported by Willis.[457] He regards this solitary plasmocytoma as probably a distinct entity and not merely as an early localized stage of multiple myeloma. He describes a focal tumor destroying the second cervical vertebra. This patient had pain localized in the cervical region for only three months; there was a history of footdrop for a period of twenty years, and the condition had been originally diagnosed as neurosyphilis. However, the Wassermann test gave negative results, and no other lesions were found at autopsy. Willis gives a good review of the literature and feels that only 13 of the reported cases of solitary plasmocytoma may be regarded with certainty. He feels that if the lesions remain solitary for a year the diagnosis is more certain. He feels that these lesions present a good prognosis with adequate operation or adequate roentgen therapy.

The literature on solitary eosinophilic granuloma is reviewed by Bass.[458] The previously reported 8 cases are reviewed, and to these the author adds 2 cases. In 1 of his patients the site of the tumor was the skull, and in the second patient, a rib. These tumors present characteristics suggestive of Hand-Schüller-Christian disease; they are well localized, rapidly growing and markedly osteolytic. One of the author's patients showed extreme eosinophilia of 11.5 per cent. The tissue section shows large cells with pale nuclei and heavy eosinophilic polymorphonuclear infiltration. Bass treated his 2 patients with wide excision and postoperative radiation. He reports no recurrence to the time of writing.

As an interesting side light to the aforementioned study, Bass[459] reports 3 cases of unusual eosinophilia in children. There was associated general adenopathy with marked leukocytosis. Without bony manifestations, these cases were regarded by Bass as probably cases of a chronic infectious condition with the definite diagnosis undetermined.

Ewing's Tumor.—There is the still continuing discussion as to the primary nature of Ewing's tumor. Colville and Willis have expressed the views that the primary nature of Ewing's tumor is unproved and that the tumor may be a metastasis from an adrenal neuroblastoma or neurocytoma.

Gharpure[460] reports a case of an untreated Ewing tumor with a complete autopsy. The lesion was primary in the femur. Its recognized

457. Willis, R. A.: Solitary Plasmocytoma of Bone, J. Path. & Bact. **53**: 77-85 (July) 1941.

458. Bass, M. H.: Solitary Eosinophilic Granuloma of Bone, Am. J. Dis. Child. **61**:1254-1262 (June) 1941.

459. Bass, M. H.: Extreme Eosinophilia and Leukocytosis: Unusual Clinical Syndrome of Unknown Origin Occurring in Childhood, Am. J. Dis. Child. **62**:68-79 (July) 1941.

460. Gharpure, V. V.: Endothelial Myeloma (Ewing's Tumor), Am. J. Path. **17**:503-508 (July) 1941.

duration was two months. At autopsy there was a solitary pulmonary metastatic nodule. There were no findings which could be regarded as primary neuroblastoma. Gharpure states that the doubt recently expressed concerning the existence of the entity of Ewing's tumor of bone is untenable.

In an article on the histogenesis Foote and Anderson [461] briefly review the literature concerning the origin of Ewing's tumor, the reticuloendothelial primitive mesenchymal cell, the lymphoblasts, the hemocytoblasts, the cells in round cell sarcoma and those of lymphangeal endothelioma.

There is a case reported of a Ewing tumor of a rib in which the histologic picture was dependable because there was no previous therapy. The section of this tissue shows definite vasoformative properties. In their opinion "the thesis of the origin of Ewing's tumor in vascular endothelium is sustained."

In the effort to find data to aid in the gradation of malignancy of Ewing's tumor, Campbell and Hamilton [462] review the clinical records and the tissue sections of 30 patients. They have not followed the usually accepted gradation of malignancy as suggested by Broders on account of the difficulty encountered by the lack of differentiation of the tumor cells. To the authors the most significant findings are the nuclear chromatin content and the cell activity as shown by the mitotic figures. They regard the larger number of chromatin knots as indicative of higher grades of malignancy. They divide the tumors into three grades according to the number of the mitotic figures in each high power field: grade 1: 1 to 5; grade 2: 6 to 10; grade 3: 11 to 15.

Of the patients with tumors of grade 1 malignancy, 31 per cent showed a five year survival rate, and 23 per cent showed a ten year survival rate. Of those with tumors of grade 2 malignancy, 33 per cent showed a survival rate of over five years, but none lived over ten years. For those with tumors of grade 3 malignancy, the prognosis was slightly over one year.

In correlating the cytologic studies with the roentgen findings, the authors feel that the bone condensation accompanies increased cellular activity in the early stages but that the late bone changes are usually accompanied by diminished cellular activity. They regard this series as too small to draw definite conclusions from, but certainly the report is an aid from the standpoint of prognosis.

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461. Foote, F. W., Jr., and Anderson, H. R.: Histogenesis of Ewing's Tumor, Am. J. Path. **17**:497-502 (July) 1941.

462. Campbell, W. C., and Hamilton, J. F.: Gradation of Ewing's Tumor (Endothelial Myeloma), J. Bone & Joint Surg. **23**:869-876 (Oct.) 1941.

An interesting study by Edwards [463] of a reticulum cell sarcoma, primary in the first lumbar vertebra, is reported together with the autopsy findings. The author describes 17 previously reported cases and adds 1 of his own. These tumors occur mostly in adolescents and young adults. The sites most commonly involved are the femur, the tibia and the clavicle. Roentgen characteristics are not sufficiently clearcut for definite diagnosis. These tumors are regarded as malignant, but the prognosis is relatively good.

Synovial Sarcoma.—The most valuable contribution on synovial sarcoma in the literature of the past year is a clinical and pathologic study of this tumor in joints, bursas and tendon sheaths by De Santo, Tennant and Rosahn.[464] Their study includes a brief historical review with a report of 16 cases. They divide synovial sarcoma into three types: encapsulated, circumscribed and diffuse. The encapsulated sarcoma arises most often in the periarticular bursas; the circumscribed tumor is in bursas or tendon sheaths, and the diffuse tumor is found most frequently in the knee. Grossly these tumors are usually soft and myxomatous with focal areas of calcification, chondrification and ossification. About half of the 37 cases reported have occurred in knee joints. Trauma and a preexisting bursitis were frequent factors in causation. The average age of occurrence was 34 years, and most patients were male. There were symptoms of mild pain in 50 per cent; the tumor was evident in over half for an average of twenty-nine months. Dysfunction was common, and swelling occurred in a few cases of intra-articular tumor. The average duration of symptoms was thirty-six months. On roentgen study there is apparent soft tissue tumor with occasional irregular calcification.[465] The usual treatment is excision; this is frequently followed by recurrence of metastasis. Delayed amputation gives the same type of result. The effect of roentgen therapy has not yet been evaluated. De Santo, Tennant and Rosahn recommend: first, widespread excision of the encapsulated tumors with deferring of amputation until the first evidence of recurrence of the tumor; second, the treatment of inaccessible tumors by immediate amputation; third, roentgen therapy, which may retard the growth of some tumors and may be of value after excision of the tumor.

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463. Edwards, J. E.: Primary Reticulum Cell Sarcoma: Case with Autopsy, Am. J. Path. **16**:835-844 (Nov.) 1940.

464. De Santo, D. A.; Tennant, R., and Rosahn, P. D.: Synovial Sarcomas in Joints, Bursae, and Tendon Sheaths: Clinical and Pathological Study of Sixteen Cases, Surg., Gynec. & Obst. **72**:951-981 (June) 1941.

465. Aitken, A. P.: Roentgenographic Recognition of Synovioma, J. Bone & Joint Surg. **23**:950-952 (Oct.) 1941.

In discussing the tumor from the histologic point of view, the authors state that the synovial cells are related to the reticuloendothelial system and are capable of three functions, viz., formation of endothelial lining, mucin and histiocytes. Multiple sections of the tumors are necessary because the tumor may be heterogenous, may have epithelioid glandlike spaces, may be pavement-like with mucin production or may be grossly myxomatous. The histiocytic type resembles the reticulum cell sarcoma and the polymorphous sarcoma with sheets of xanthomatous cells. Any fibrosarcoma or spindle cell sarcoma in or near a joint is likely to be synovial sarcoma; the proof depends on painstaking pathologic investigation. The least malignant of these tumors show a high degree of histiocytic differentiation, while the most malignant are probably those with closely packed round oval cells with abundant reticulum.

A similar report of 4 cases of synovial sarcoma is made by Jaffe and Lichtenstein.[466]

Herzmark [467] reports a giant cell synovial tumor of the knee treated by excision. This was followed in six months by recurrence: after roentgen therapy there was no more trouble for at least one year. [ED. NOTE: This was probably a synovioma, although no mention of mitosis is made in the pathologic report.]

Hutchison and Kling [468] present a case report of malignant synovioma in the knee treated by excision and roentgen therapy. The patient died at the end of seven years. This tumor was of the solid type and consisted mostly of spindle cells.

Leichner and Schaefer [469] report a case of synovial sarcoma arising from the gluteal bursa in a 10 year old girl. They state that radical amputation is essential and that roentgen therapy is of no value.

Herson [470] reports a benign synovioma arising in one of the bursas about a knee. This followed trauma. On histologic study this tumor was benign, and fifteen months after excision there had been no recurrence.

The roentgen recognition of synovioma is discussed by Aitken,[465] who states that a provisional diagnosis of synovioma can be made when

466. Jaffe, H. L., and Lichtenstein, L.: Sarcoma (Synovioma), Bull. Hosp. Joint Dis. **2**:3-10 (Jan.) 1941.

467. Herzmark, M. H.: Giant Cell Synovial Tumor of Knee, J. Bone & Joint Surg. **23**:684-686, (July) 1941.

468. Hutchison, C. W., and Kling, D. H.: Malignant Synovioma, Am. J. Cancer **40**:78-84 (Sept.) 1940.

469. Leichner, W., and Schaefer, A.: Synovial Sarcoma: Case Report, Connecticut M. J. **5**:113-115 (Feb.) 1941.

470. Herson, R. N.: Benign Synovioma Arising in Bursa, Brit. M. J. **1**:52 (Jan. 11) 1941.

the tumor mass is rounded, lobulated and sharply defined and contains scattered or irregular deposits of amorphous lime. He presents a case report in which the patient was a 21 year old man with a definite history of trauma two years preceding the development of the tumor.

A giant cell xanthoma is reported by Conzett and Young.[471] Their patient was a 63 year old white man in whom after trauma to the wrist a mass developed on the dorsum. This mass had been present for five years. The tumor surrounded the tendons of the extensor of the thumb and the index finger. The histologic diagnosis was giant cell xanthoma of the tendon sheath, and there had been no recurrence nine months after excision.

Metastatic New Growths in Bone.—The clinical syndrome and the early diagnosis of metastatic carcinomatous lesions of the spine are well portrayed by Wolfson, Reznick and Gunther.[472] They believe that early diagnosis can be made before changes in the bone are evident on roentgen examination. They state that at least 1 sq. cm. of the vertebral body must be destroyed before the changes are apparent in a roentgenogram. They stress pain as the earliest symptom. It is the characteristic root pain limited to a definite dermatome aggravated by sudden jarring, sneezing or bending. The zone is narrower in cases of arthritis. It is constant as contrasted with the intermittent pain of arthritis or myositis and neuralgia. In cases of arthritis motion does give some relief at times. This is not true of the pain due to metastatic carcinoma. The percussion tenderness over the spine is constant. The authors insist that there is persistent elevation of the sedimentation rate in those cases in which there are bone metastases; they state also that the phosphatase level is high with the osteoblastic lesions and high or normal with the osteoclastic lesions. In their experience early roentgen therapy affords relief; hence early diagnosis of metastasis is important.

In considering the differential diagnosis of carcinoma of the prostate with skeletal metastasis and osteitis deformans, deVries[473] writes particularly from the urologic viewpoint. It is his opinion that a digital prostatic examination suffices to make a diagnosis of carcinoma of the prostate in 90 per cent of the cases of this type. In the remaining cases

471. Conzett, D. C., and Young, E. R.: Giant Cell Xanthoma of Wrist, J. Iowa M. Soc. **31**:29-31 (Jan.) 1941.

472. Wolfson, S. A.; Reznick, S., and Gunther, L.: Early Diagnosis of Malignant Metastases to Spine: Clinical Syndrome, J. A. M. A. **116**:1044-1048 (March 15) 1941.

473. deVries, J. K.: Differential Diagnosis of Carcinoma of Prostate with Skeletal Metastases and Osteitis Deformans (Paget's Disease of Bone), J. Urol. **46**:981-996 (Nov.) 1941.

cystoscopy, cystourethrography and biopsy may be necessary to confirm the diagnosis. He demonstrates well the punch aspiration biopsy as a diagnostic procedure.

Adenocarcinoma of the male breast of the scirrhous type with generalized bone metastasis is reported by Livingston.[474] The patient had extremely widespread osteolytic metastasis. [ED. NOTE: Geschickter and Copeland report only 1 case of metastatic lesion in a male patient in 100 cases of cancer of the breast.]

A rare leukemoid reaction in a case of carcinomatous skeletal and splenic metastasis from bronchiogenic carcinoma is reported by Lisa, Solomon and Gordon.[475] There are extremely few cases of metastatic carcinoma reported in which immature myeloid cells are noted frequently in the circulating blood. In this case of bronchiogenic carcinoma with metastasis there were leukemoid reaction, purpura and relative and absolute lymphocytosis. The tumor and the metastases were anaplastic with cords of cells and diffuse invasion without real tumor formation. [ED. NOTE: These cases are of interest so far as the blood picture may confuse the diagnosis.]

Squamous cell carcinoma arising in a chronic osteomyelitic sinus tract and developing metastatic lesions is shown in 2 cases by Bereston and Ney.[476] They have reviewed the literature well and added these 2 new cases. Malignant degeneration in chronic osteomyelitis from sinus tracts occurs in men 40 to 60 years of age with a history of osteomyelitis from a sinus tract of twenty to thirty years' duration. The bones most commonly affected are the tibia, the femur and the bones of the hand. The local signs are a cauliflower mass or a foul discharge from the deep sinuses. The lesions are proved by biopsy and roentgen examination. Metastasis from this type of carcinoma is rare, only 7 cases having been previously reported. Of the 2 cases added, in one there was metastasis to the lung, in the other, to the pelvis. The rarity of metastasis in this type of lesion is explained by the low grade of malignancy or by the possibility that some of the cases of carcinoma reported may have been instances of pseudoepitheliomatous hyperplasia rather than of true malignant tumor.

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474. Livingston, S. K.: Adenocarcinoma, Scirrhous Type of Left Male Breast with Generalized Bone Metastasis: Case Report, Am. J. Roentgenol. **45**:589-590 (April) 1941.

475. Lisa, J. R.; Solomon, C., and Gordon, E. J.: Leukemoid Reaction in Carcinomatous Skeletal and Splenic Metastases: Case Report, Am. J. Cancer **40**:227-230 (Oct.) 1940.

476. Bereston, E. S., and Ney, C.: Squamous Cell Carcinoma Arising in Chronic Osteomyelitic Sinus Tract with Metastasis, Arch. Surg. **43**:257-268 (Aug.) 1941.

In the literature on malignant tumors of the parathyroid gland as reviewed by Gentile and associates,[477] 21 cases have been reported. These authors report a case of malignant disease of the parathyroid with local metastasis and multiple pathologic fractures. Five years after removal of the parathyroid tumor the patient was alive and well. The fractures were well healed, and there was moderate recalcification of bone.

The roentgen manifestations of skeletal metastasis from neuroblastoma are presented by Ackermann [478] in his report of 4 cases. This is a fairly complete discussion of a rare entity. The embryologic development of the sympathetic nervous system is shown to be of the same origin as that of the medulla of the adrenal gland. Neuroblastomas arise from sympathetic neuroblasts, which are undifferentiated migratory cells. These arise in the adrenal medulla or the adjacent sympathetic ganglions. Neuroblastoma occurs in children, usually while they are under 3 years of age. According to the distribution of metastasis there are two types. In one type metastasis is found in viscera and later in the flat bones. In the other type there is metastasis to the skull first; there is local swelling, proptosis, discoloration of the eyelid and profound secondary anemia. The course is rapidly fatal. The roentgen appearance is that of an osteolytic tumor with periosteal reaction similar to Ewing's tumor or osteogenic sarcoma. The differential diagnosis with regard to syphilis or chloroma may be extremely difficult.

A review of the literature on subungual melanoma is made by Scannell [479] in connection with the report of a single case. He states that the incidence is 1 in 18,752 new hospital admissions. It is uncommon in Negroes. It occurs more frequently in older people. There is a history of trauma in more than one half of the cases. The lesion begins as a paronychia and often develops as a black fungating ulcer elevating the nail. There is a pathognomonic coal black border along the edge of the nail involved. The dressings are often stained brown. The growth is usually slow, spreading to the inguinal and axillary nodes first. Then it may go to wide metastasis. On microscopic examination there are two types of cells, the spindle and the polygonal with alveolar arrangement. The tissue is friable, and frozen sections are difficult. The author advises amputation with resection of the regional glands as the treatment of

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477. Gentile, R. J.; Skinner, H. L., and Ashburn, L. L.: Malignant Tumor with Osteitis Fibrosa Cystica: Parathyroid Glands, Surgery **10**:793-810 (Nov.) 1941.

478. Ackermann, A. J.: Neuroblastoma, with Special Reference to Roentgen Manifestations, J. Oklahoma M. A. **34**:241-246 (June) 1941.

479. Scannell, R. C.: Subungual Melanoma: Report of Case, Am. J. Surg. **53**:163-167 (July) 1941.

choice. These tumors are radioresistant. Five year survival rate is about 25 per cent.

An amelanotic melanoma is reported [480] which is regarded as a non-pigmented mole. The ulcerating mass was removed from the toe in 1923. In 1938 the patient returned with metastasis in the femoral nodes. These metastases became widespread to the skin, the tonsils, the heart, the mediastinum, the omentum and the adrenals. This case is confusing from its beginning.

New Growth Superimposed on Previously Existing Pathologic Growth.—Bennett and Berkheimer [481] report on malignant degeneration of multiple benign exostosis in a boy with anaplastic changes in a benign osteoma of the lower end of the femur. They present a genetic history showing many benign exostoses in the family but no definite mendelian pattern and no cases of malignant exostosis. In a nephew of this patient a comparable benign tumor was demonstrable at the age of 5 months. The authors in their discussion show a distinct relation of this group of tumors to chondroma or enchondroma. From their review of the literature it is apparent that malignant change in multiple benign exostosis is relatively rare. The type of malignant growth encountered is usually osteogenic sarcoma, but the grade of malignancy is distinctly less than that of the malignant growth of the primary type. The treatment of choice is amputation, but high voltage roentgen therapy is of value if amputation is not permissible.

There are two interesting articles on osteosarcoma with extraskeletal bone formation bearing a close resemblance to osteogenic sarcoma. Mayer and Friedman [482] report a painful swelling in the calf of the leg of a 17 year old girl, existing for five weeks and growing rapidly with no history of trauma. From the site of the tumor there was removed a large sheet of fascia, thick, firm in consistency and having a central marble-like mass of bone. The tissue was studied by four pathologists, each reporting an osteogenic sarcoma. Amputation was done through the lower third of the thigh, and for eight years there was no evidence of recurrence. In view of the benign course of the disease the authors doubt the diagnosis of osteogenic sarcoma and call attention to the close

480. Amelanotic Melanoma: Case Report, Connecticut M. J. **5**:193-196 (March) 1941.

481. Bennett, G. E., and Berkheimer, G. A.: Malignant Degeneration in Case of Multiple Benign Exostoses with Brief Review of Literature, Surgery **10**:781-792 (Nov.) 1941.

482. Mayer, L., and Friedman, M.: Extra-Skeletal Bone Forming Tumor of Fascia, Resembling Osteogenic Sarcoma, Bull. Hosp. Joint Dis. **2**:187-192 (Oct.) 1941.

resemblance of this tissue to the metaplastic benign tumors described by Mallory. Two others were described by Geschickter and Maseritz. Mayer and Friedman state:

> The lesion is an atypical form of myositis ossificans and arises apparently from a young fibroblast, which by the process of metaplasia, differentiates into various types of connective tissue elements, including osteoid tissue and bone. . . . The absence of atypism, tumor giant cells, or a significant number of mitotic division figures rules out an osteogenic sarcoma.

Wilson [483] reports 10 cases of extraskeletal ossifying tumors or osteosarcoma. In this group there were 4 osteogenic sarcomas, 1 fibrosarcoma, 1 chondrosarcoma, 1 bursal sarcoma with ossification, 1 case of von Recklinghausen's disease with ossification in a neurofibroma and 2 fibrous osteomas. The author feels that the potency of neoplastic mesoblastic tissue goes in almost any direction; also, that myositis ossificans offers the most difficulty in distinguishing heteroplastic from neoplastic bone formation.

A fibrosarcoma developing in the scar of an old burn is described by Fleming and Rezek.[484] The scar had existed for forty-nine years. Wide excision of the tumor with a skin graft covering the defect was done. Regional gland metastasis developed, and the patient died nineteen months after the operation. Autopsy showed visceral metastasis as well. These authors state that there have been 2 other sarcomas which developed in the skin after trauma.

Zieman [485] reports a tumor on the tip of a finger within a few months after trauma. Four years after this trauma the tumor was resected and showed microscopically "a fibrogenic fibrocellular sarcoma."

In this group of cases could well be included an ossifying fibroma of the thenar space reported by Kyle.[486] The pathologic growth reported was that of an ossifying fibroma; more detailed history was not given.

A case of meningeal tumor with both osteoblastic and osteoclastic activity was related by Turner and Craig.[487] This is a single case report, but it is accompanied by a good discussion of bone formation and soft

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483. Wilson, H.: Extraskeletal Ossifying Tumors, Ann. Surg. **113**:95-112 (Jan.) 1941.

484. Fleming, R. M., and Rezek, P. R.: Sarcoma Developing in Old Burn Scar, Am. J. Surg. **54**:457-465 (Nov.) 1941.

485. Zieman, S. A.: Fibrosarcoma of Soft Parts of Extremities, Surgery **9**:675-678 (May) 1941.

486. Kyle, B. H.: Ossifying Fibroma in Thenar Space: Case, Virginia M. Monthly **68**:165 (March) 1941.

487. Turner, O. A., and Craig, W. M.: Osteogenic Sarcoma of Meningeal Origin: Case of Meningeal Tumor with Both Osteoblastic and Osteoclastic Activity, Arch. Path. **32**:103-111 (July) 1941.

tissues. The authors feel that in this case there was sarcomatous transformation of the fibroblastic connective tissue of the tumor. They regard this as rather rare, because most of these processes ordinarily show heteroplastic formation of bone.

In reporting a case in which autopsy was done, Curphey [488] describes diffuse pagetoid osteitis complicated by an osteogenic sarcoma in a patient with syphilis. There were definite syphilitic changes in all organs. Paget's osteitis was atypical with sarcomatous and presarcomatous osteoid tissue in the intratrabecular spaces. The author's diagnosis is pagetiform syphilis of bone with secondary sarcomatous changes. In his review of the literature on Paget's disease in persons with syphilis, he states that all lack histologic proof that the bone changes are not typical of osteitis deformans.

Tumors of the Spinal Cord.—In reporting a case of dermoid tumor extending from the second lumbar to the second sacral segment in a boy of 9 years, Bagley and Arnold [489] have selected from the literature 44 cases of intraspinal dermoid and 13 of teratoma. They discuss the unusual symptoms of cauda equina tumor and stress the observation that spasm of the erector spinae and hamstring muscles are suggestive of early signs of cauda equina tumor.

Another rare but interesting entity is a case of von Recklinghausen's neurofibromatosis with an hourglass tumor of the cervical spine reported by Jelsma.[490] This tumor was dumbbell in form with a portion intraspinal and a portion extraspinal and with a connecting portion through the intervertebral foramen or interlaminar space. There are eight references to the literature representing the reports of 89 cases. These tumors occur most commonly in the thoracic portion of the spine, only 22 having been reported in the cervical portion of the spine. They are usually benign, originating from meninges, a nerve root or rarely a ganglion. Intraspinal portions are small, about the size of a hazelnut. The extraspinal portions are the size of a plum or an orange. Eighty per cent of these tumors are visible or palpable in the anterior or the posterior triangle of the neck. The origin and the development of this

488. Curphey, T. J.: Report of a Case of Diffuse "Pagetoid" Osteitis in a Syphilitic Complicated by Osteogenic Sarcoma, Urol. & Cutan. Rev. **45**:438-443 (July) 1941.

489. Bagley, C., Jr., and Arnold, J. G., Jr.: Unusual Symptomatology of Cauda Equina Tumors: Report of Case of Dermoid with Review of Literature of Dermoid and Teratomatous Tumors of Vertebral Canal, Tr. Am. Neurol. A. **66**:171-175, 1940.

490. Jelsma, F.: Hour-Glass Tumors of Cervical Spine, Am. J. Surg. **52**: 483-488 (June) 1941.

tumor are uncertain. The symptoms are those of spinal cord compression, and roentgenograms often show an enlargement of the intervertebral foramen.

Surgical Treatment.—During the past few years there has been a growing tendency toward conservative operation in the treatment of benign tumors of bone and of those malignant tumors of bone of low malignancy and so situated that excision of the tumor can be done with immediate or early replacement by bone grafts. Coley [491] reports 8 cases together with the roentgen findings. In his opinion the growths suitable for conservative operation are the bone cysts, the giant cell tumor, the central chondroma (in spite of its tendency to recurrence) and a few osteogenic sarcomas of low grade malignancy.

Phemister [492] recommends the use of the bone graft in cases of giant cell tumors, in rare cases of early well localized sarcoma and in cases in which amputation is refused. He feels there is a definite place for this type of operation in the treatment of malignant tumors of bone which are centrally located and are of low malignancy and of which an early diagnosis is made.

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491. Coley, B. L.: Conservative Surgery in Tumor of Bone, South. Surgeon **10**:379-392, (June) 1941.

492. Phemister, D. B.: Use of Bone Graft in Treatment of Bone Tumors, Proc. Interst. Postgrad. M. A. North America (1939), 1940, pp. 24-27.

(*To Be Continued*)

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